

Safeguarding the Ethical Conduct of Biomedical Research in Israel against Conflict of Interest

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Abstract

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The global entrepreneurialism of biomedical research and its close ties with the private sector have introduced strong financial incentives into the public arena. In Israel, powerful forces of privatization have strengthened the enterprise of competitive research. A pivotal concern is whether an increasingly competitive research environment will create conflicts of interest (COI) impacting researchers and research institutions' ability to protect research validity and research participants' health and safety.

In Israel, scandals have raised concerns about whether those responsible for conducting and evaluating research are committed to ethical standards. In response, the government has introduced regulatory mechanisms aimed at limiting the negative influence of commercial COI. The regulatory scheme imposes upon the hospitals and the Israeli Ministry of Health (MOH) the responsibility to identify and eliminate COI arising from the relationships between commercial sponsors and investigators. The scheme also calls for screening to determine eligibility of government advisors used for scientific input in the review of new trial applications.

This dissertation evaluates whether government-created mechanisms are adequate responses to commercial incentives in the otherwise self-regulated research landscape in Israel. The collection and analysis of empirical data reveals practical interpretations and implementation of the regulatory mechanisms. The U.S. regulatory model illuminates a comparative model for

attending to similar COI challenges. This dissertation suggests that current Israeli regulatory safeguards are lacking crucial standards and norms. The lack of standardized objectives and responsibilities, and the substantial variations found in institutional interpretation and implementation, require further regulatory intervention by the Israeli government.

The objectives of this dissertation are to promote transparency and accountability within the Israeli biomedical scheme. The analysis is premised on the assumption that the protection of human subjects and the preservation of integrity within the context of medical research must evolve in tandem with the changing world of innovation and creative technologies. Securing legitimate standards and norms will benefit not only the research community, but also the welfare of the general public and those who contribute to scientific inquiry as clinical trial participants.

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CHAPTER 1: Entrepreneurialism of Biomedical Research and Conflict of Interest: Protecting Ethical Principles in Israel

“Ultimately, the spirit in which an aware society undertakes to use human beings for research ends will determine the protection which those human beings will receive. Therefore, we have urged throughout a greater participation by society in the decisions which affect so many human lives.”¹

1.1 Introduction

1.1.1 Background - Entrepreneurialism of Biomedical Research and Conflict of Interest

The biomedical industry has for several decades been one of the most rapidly growing sectors in the world economy. Pharmaceutical drugs, biologics, and medical devices are used to fight disease, improve the quality of life, and increase life expectancy. Developing new therapeutics requires a substantial investment in R&D. According to a 2008 U.S. Department of State report, the average cost of developing new drugs can range from \$800 million to nearly \$2 billion per approved drug.² R&D spending in biopharmaceutical research within the U.S. alone reached \$65.2 billion in 2008.

Notwithstanding the high costs of developing innovative medical products and therapies, the return on investment has been consistently on the rise. In the U.S. alone, the economic return of the U.S. investment in medical research in terms of improving health and life expectancy are estimated at more than \$500 billion per year.³ There is little doubt that substantial profits are an inducement to the development of new discoveries aimed at improving human health and wellbeing.

¹ Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel Charge III, U.S. Dep't. of Health, Educ. & Welfare, Pub. Health Serv. (1973), available at biotech.law.lsu.edu/cphl/history/reports/tuskegee/tuskegee.htm (last visited Sept. 7, 2012).

² Neal Masia, *The Cost of Developing a New Drug: New Wonder Medicines Come from Years of Research, High Costs* (April 2008), available at <http://www.america.gov/st/econ-english/2008/April/20080429230904myleen0.5233981.html> (last visited Sept. 7, 2012). Also see JF Peipert, *The economic value of medical research: is it worth the investment?*, *Obstet Gynecol* 99(5 Pt 1):835-40 (2002).

³ *Id.*

The multinational pharmaceutical and biotechnology industry takes on or supports the vast majority of discoveries and development of new therapeutics.⁴ The funding of medical research by the for-profit industry has been increasing worldwide, while government or public support had been decreasing. According to the OECD report from 2010⁵, approximately two thirds of science and technology R&D expenditure is funded by the private sector.⁶ In fiscal year 2008, in countries such the U.S., Germany, Finland and Japan, business enterprise financed more than two-thirds of all R&D investments. In China and Israel the business financed R&D in 2008, at 70 percent and 77 percent respectively.⁷ Although Israel has one of the highest national percentages of private sectors R&D funding of all OECD members, it also had the highest gross expenditure of its GDP on R&D in 2008.⁸ Particularly in medical research, a report shows that the industry support of clinical research in Israel had been on the rise. The biggest increases were in 2006-2007 when investment rose approximately twenty six percent each year. In 2010, compared to the previous years, there was a slight decline. In 2009 and 2010 the private biomedical sector invested approximately eighty million dollars in clinical trials in Israel.⁹

The biomedical industry is fueled by basic medical discoveries developed within the realms of academic research institutions or publicly funded research. The systematic and strong collaborations between academic researchers, publically funded institutions and industry are a crucial element for a potentially successful commercialized breakthrough. At the same time, along with enhancing innovations and generating commercialization, these close collaborations also generate divergent allegiances among the various R&D stakeholders.¹⁰ Mainly, these close

⁴ See Thomas M. Jacobsen et al., *Modern Pharmaceutical Industry: A Primer* (2010).

⁵ See Org. for Econ. CO-Operation & Dev., *OECD Science, Technology & Industry Outlook* (2010) (hereinafter OECD), available at http://dx.doi.org/10.1787/sti_outlook-2010-en (last visited Sept. 7, 2012).

⁶ According to the OECD report, since 2004 the percentage of the R&D expenditure funded by the private sector had risen from 62.1 percent to 64.5 percent as of 2008. At the same time, R&D funded by the government decreased from 30.3 percent to 27.6 percent. *Id.*

⁷ Notwithstanding the above, in some countries, such as Greece and Poland, the business enterprises had financed less than one-third of these countries' R&D. *Id.*

⁸ Business expenditure on R&D was 3.9 percent of GDP in 2008, more than in all other member countries. *Id.*

⁹ Roni Linder-Gantz, *Hamerkazing Harefuieem Hervichu 282 Million NIH Memechkar Clini Be 2010* (The Medical Centers Earned 282 million NIH from Clinical Research), *The Marker* (March 17th 2011) available at <http://www.themarker.com/news/1.605979> (last visited Sept. 7, 2012). As will be discussed in the following chapters, this only represent a partial picture of the industry's investment in Israel as the data obtained from the Israeli Ministry of Health only relate to government owned hospitals and hospitals owned by one of the health plan – Clalit. Other hospitals are not required to provide data to the ministry of health.

¹⁰ See Tom L. Beauchamp & James F. Childress, *Principles of Biomedical Ethics*, 12 (5th ed. 2001).

partnerships create obligations for trial sponsors and raise intellectual property issues that may clash with academic and scientific values.

Contrary to the scientific paradigm of free, objective inquiry and free simulation of knowledge, the biomedical research industry has a powerful financial interest in the success of research.¹¹ Many analysts have argued that the competitive and profit-driven nature of the medical science industry is at odds with the objectivity ethos.¹² A robust empirical and scholarly study conducted in the last two decades has suggested that financial conflict of interest (COI) in biomedical research has been associated with a number of concerning research practices. These studies have shown, inter alia, increased likelihood of pro-industry findings, withholding negative results from publication, restricting investigator's publication, and implementing biased study designs.¹³ Substantial studies demonstrate significant funding influences on research findings and promote research bias. For example, studies published in various medical journals showed that privately sponsored research will more likely favor the sponsor's product, as opposed to a similar study funded by nonprofit or government agency.¹⁴

Notwithstanding the studies suggesting pro-industry research outcomes, different studies report that individual researchers have increasingly sought to enhance their own financial interests in the studies they conduct. More and more investigators seek financial gain from their new discoveries with commercial potential. For instance, a study of biomedical researchers in the U.S. found that about twenty two percent had applied for patents within the last few years, and twenty five percent participated in corporate pursuits.¹⁵ Not only are individual investigators interested in the potential high equity stakes involved, but also academic and nonprofit research organizations want their share as well. A 2003 survey reported that about two thirds of U.S. academic medical centers hold equity rights in companies that fund research within the same

¹¹ Gordon Du Val, *Research Ethics: Institutional Conflicts of Interest: Protecting Human Subjects, Scientific Integrity, And Institutional Accountability*, 32 *J. L. Med. & Ethics* 613 (2004).

¹² For example see Cinead R. Kubiak, *Conflicting Interests & Conflicting Laws: Re-Aligning the Purpose and Practice of Research Ethics Committees*, 30 *Brooklyn J. Int'l L.* 759 (2005).

¹³ See Kanu Okike et al., *Accuracy of Conflict-of-Interest Disclosures Reported by Physicians*, 361 *New Eng. J. Med.* 1466 (2009).

¹⁴ In their book Shamoo and Resnik provide a long list of empirical studies suggesting potential research bias. See Adil E. Shamoo & David B. Resnik, *Responsible Conduct of Research*, 189-190 (2003).

¹⁵ Ron Bouchard, *Balancing Public and Private Interests In The Commercialization of Publicly Funded Medical Research: Is There a Role For Compulsory Government Royalty Fee?* 13 *B.U.J. SCI. & TECH. L.* 120 (2007).

institution.¹⁶ Most academic institutions have technology transfer offices facilitating revenues from intellectual property.¹⁷ Universities in the U.S., for example, generated much more income from patent licensing in 2000 (997 million USD) than in 1991 (121 million USD).¹⁸

These findings have raised questions regarding the design and reports of industry sponsored biomedical research, as well as legal or ethical concerns for misconduct and bias. As data suggest, for several decades the biomedical professionalism had been progressively corroded by multifaceted financial ties between physicians, academic researchers, research institutions and the pharmaceutical, medical device and biotechnology industries. Nevertheless, these financial ties were seldom subject to any significant COI commentaries by the media or the public before the 1990s. The former editor-in-chief of the *New England Journal of Medicine*— Jerome Kassirer was surprised by the lack of public oversight regarding doctors’ potential COI before the 1990s. He asks: “How could a profession on which health care so critically depends be so undervalued?”¹⁹

Critics are concerned with how much and how deep the biomedical research decision-making processes and practices are tainted by COI. Dr. Marcia Angell, a former editor-in-chief of the *New England Journal of Medicine* and a current lecturer at Harvard Medical School, believes that it has gone too far. Dr. Angell warns that: “Similar COIs and biases exist in virtually every field of medicine, particularly those that rely heavily on drugs or devices. **It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines.**”²⁰ [Emphasis provided] In view of the fact that essentially every aspect of clinical research is driven by human decision-making, it is worrisome that virtually any aspect of research can be affected by COI. COI

¹⁶ Justin E. Bekelman et al., Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A systematic Review, *JAMA* 454 (2003).

¹⁷ In the U.S. for example, the Bayh-Dole Act of 1980, goal was to encourage commercialization of academic discoveries as the Act allows researchers and research institutions the option under certain circumstances to retain the IP rights of their discoveries for government funded research. This act was codified as 35 U.S.C. §200-212.

¹⁸ See David Blumenthal, Academic-Industrial Relationships in the Life Sciences, *N. Engl. J. Med.* 349, 2452-2459 (2003).

¹⁹ See Jerome P. Kassirer, *Foreword* to Marc A. Rodwin, *Conflicts of Interest & the Future of Medicine*, at ix-xi (Oxford 2011).

²⁰ See Angell, Marcia, *Drug Companies & Doctors: A Story of Corruption*, N.Y. Rev. Books, Jan. 15, 2009, available at <http://www.nybooks.com/articles/archives/2009/jan/15/drug-companies-doctors-a-story-of-corruption/>, (last visited Sept. 7, 2012).

circumstances arise where individual or institution's financial, political or other interests are likely to undermine their ability to carry out their professional, legal and ethical obligations.²¹ COI can affect all biomedical research areas and result in potential violations of ethical rules and principles.²²

On the other hand, many scholars and clinical investigators argue that financial interests provide powerful incentives for medical advances and innovation. In fact, they maintain that enabling and promoting technology transfer and a close relationship between academia and industry fuels the rapid growth of the biotech sector.²³ Arguably, prohibiting or restricting financial incentives will hinder medical progress and impede the ability to fight disease, improve the quality of life, and increase life expectancy. Notably, even those who strongly object to the close ties with industry do not call to eliminate them completely.

Scholars worldwide debate the nuanced distinctions of what is deemed appropriate collaboration or financial ties within the context of biomedical professionalism, which makes discussion of COI even more complicated. Contrary to the widespread focus in public discourse on the corrupting influence of COI, the nature of COI debate within the medical research field is dramatically different. COI in medical research has been defined as circumstances where professional judgment or action concerning primary interest will be overly influenced by a secondary interest.²⁴ In biomedical research the primary interest includes protecting participants'

²¹ See Shamoo & Resnik *supra* note 14 at 193 for the discussion of individual COI and at 195-198 for institutional COI.

²² On August 2010, Dr. Steven Joffe, an associate professor of Pediatrics at Harvard Medical School and a medical member of the Pediatric Oncology at the Dana-Farber Cancer Institute in Boston, gave a presentation at the Fred Hutchinson Cancer Research Center called "Financial Relations With Industry: Even More Challenging Than We Thought". In his presentation, Dr. Joffe described the vital mechanisms in clinical trial as it flow from the health need, to study design, conduct, analyze and interpretation to report, collate evidence to the ultimate goal of improving clinical practices. Dr. Joffe showed how practically all trial aspects can be biased and can impact the research outcomes. For example, the choice of control group – inactive or active group – based on a study conducted in 1996-8 for multiple myeloma trials. The study showed that while the industry sponsored trial preferred using inactive control group favoring the new treatment by far, the non-industry studies favored active control which favored the control over the new treatment. In other words, the decision whether to use inactive or active control in clinical trials have major implications on the study results.

²³ For more discussion on the scholars' debate regarding the management of financial COI, please see Mark Barnes & Patrik S. Florencio, Symposium: New Directions in Human Subject Research: Looking Beyond the Academic Medical Center: Investigator, IRB and Institutional Financial Conflicts of Interest in Human-Subjects Research: Past, Present and Future, 32 *Seton Hall L. Rev.* 525 (2002).

²⁴ See Dennis F. Thompson, Understanding Financial Conflicts of Interest, *N. Engl. J. of Med.* 329, 573-576 (1993).

health, research validity and maintaining the public trust.²⁵ Whereas the secondary interest may include financial interests resulting from the collaboration with industry or equity holding; and non-financial interests, such as pursuing professional advancements, reputations etc. As opposed to the traditional discourse of COI in the political context, in medical research the secondary interests themselves are not considered to be illegitimate, as some are considered desirable professional practices.²⁶ The specific concern in biomedical research focuses on whether such secondary interests can create biases in researchers and in institutional decision-making practices and processes that can in turn jeopardize the health of research subjects and research integrity.²⁷

The distinct and unique nature of COI in medical research is illustrated in the following three aspects:

- 1) In medical research, fundamental inherent conflict exists between the investigators' duty to pursue scientific inquiry for the sake of the public at large, and their obligation to safeguard the health and welfare of their patients and participants.²⁸ In fact, this profound conflict was the primary reason why U.S. policymakers insisted on having independent ethical evaluations by ethics committees.²⁹ In the traditional political form of work, public officials have no inherent conflict as their duty centers on their obligation to serve the public.
- 2) There is a wide consensus, even amongst critics, that collaboration between academia and industry is the engine for innovation. In the traditional form of public service, any collaboration with private industry for private interest is commonly restricted or prohibited.

²⁵ *Id.*

²⁶ These legitimate secondary interests may include scientific recognition and grant support. See EJ. Emanuel & D. Thompson, the Concept of Conflicts of interest in Medical Research: Historical developments in The Oxford Textbook of Clinical Research Ethics, 760 (Emanuel E. at el. ed. Oxford 2008).

²⁷ Robert Gatter, Conflicts of Interest in International Human Drug Research and the Insufficiency of International Protection, 32 Am. J. L. & Med. 351 (2006).

²⁸ The U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in addressed this inherent conflict in their 1978 report. See Institutional Review Boards: Report and Recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 43 Fed. Reg. 56,186 (November 30, 1978).

²⁹ Trudo Lemmens, Conflict of Interest in Medical Research: Historical developments in The Oxford Textbook of Clinical Research Ethics, 747-757 (Emanuel E. at el. ed. Oxford 2008).

- 3) COI in medical research can create biases in researchers and/or in institutional decision-making practices and processes that can jeopardize the health and safety of research subjects and future patients.³⁰ Risks associated with COI in public office usually relate to pecuniary damage and typically affect the specific subject matter.

Due to distinct aspects of COI in clinical trial settings, we should be mindful of whether and how to apply the traditional political COI doctrine. Biomedical research theories and policies should be tailored to the unique characteristics of the COI in accordance with the country's political, legal and cultural norms. For the purpose of definition it is also important to distinguish between COI and conflict of commitment. As oppose to COI, conflicts of commitment typically do not involve circumstances where professional judgment might be compromised.³¹ Conflict of commitment is primarily concerned with employees' ability to comply with their work responsibilities in light of the employees' outside commitments: the concern relates to issues constraining time and efforts.³²

Generally, COI is prevalent in medical research and medical practice in various countries regardless of their diverse medical, economic and political systems. Addressing the unique characteristics of COI, several guidelines and regulations have been developed by various national and international bodies aimed at ascertaining the general ethical principles governing biomedical research involving human subjects.³³ Dennis Thompson, a well known scholar and professor at Harvard University, argues that the growing role of government regulating COI is partly due to the greater stake that society has in medical practice and research in its role as potential research participants and medical patients.³⁴

³⁰See Gatter *supra* note 27.

³¹ Shamoo and Resnik *supra* note 14, at 193.

³² See Inst. of Med., Conflict of Interest in Medical Research, Education & Practice, 46-48 (Bernard M. Lo & Marilyn J. Field eds., 2009) (hereinafter: The IOM report).

³³ The Declaration of Helsinki by the World Medical Association, for example, acknowledged this conflict and thus requires investigators to conduct a thorough risk/benefit analysis along with a detailed informed consent processes. See the World Med. Asso., Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects (2008), available at www.wma.net/e/policy/b3.htm (last visited Sept. 7, 2012). (hereinafter: the Declaration of Helsinki).

³⁴ Thompson Dennis F., Restoring Responsibility: Ethics in Government, Business & Healthcare 295-297 (Cambridge 2005).

Within the context of a clinical trial, COI circumstances require careful evaluation as to what extent, if at all, the conflicted interest is deemed proper in accordance with the relevant existing regulatory scheme approach. In order to assess that, one must review and comply with all procedural requirements as necessitated within the relevant regulatory regime and the general principles of research ethics. However, despite strong international agreement on the significance of identifying and managing COI in medical research, there is no shared global definition of conflicts of interest, mechanisms or processes to manage COI. Thus, each country addresses potential COI in medical research conducted within their borders through different legal and governance arrangements.

1.1.2 COI in Biomedical Research – The Israeli Case

Generally, the Israeli regime requires hospitals and the Ministry of Health (MOH) as part of their regulatory role as evaluators of potential ethics violations, to review and eliminate COI situations arising from the financial or contractual relationships between trial sponsors and investigators.³⁵ As of 2009, the regulatory scheme also imposes COI screening procedures for eligibility of government advisors used by the MOH. The question of whether the regulatory system and its ethics reviews are well-equipped to protect against ethical and legal violations took center stage in Israel. A well-publicized report issued by the State Comptroller in 2004 brought to light serious ethical and legal violations, some of which involved COI issues.³⁶ The adequacy of the current regulatory system has been publicly called into question. This high profile incriminating report highlighted serious ethical deficiencies with respect to prestigious medical institutions. During the same period, highly publicized scandals discussed several concerning practices on part of physician-researchers. Several physician-researchers were accused in contributing to the deaths of elderly trial participants³⁷; some researchers were criminally charged with false

³⁵ See Guidelines for Clinical Trials in Human Subjects at§9 Ministry of Health Pharmaceutical Administration in Jerusalem (2006), available at [www.health.gov.il/download/pages/guidelinesclinical trialshumanEnglish.pdf](http://www.health.gov.il/download/pages/guidelinesclinical%20trialshumanEnglish.pdf) (last visited Sept. 7, 2012). (hereinafter: Guidelines for Clinical Trials).

³⁶ A copy of the State Comptroller's Report 55 (2004), available on <http://www.mevaker.gov.il/serve/contentTree.asp?bookid=426&id=2&contentid=7933&parentid=undefined&bctype=7932&sw=1280&hw=954> (last visited on Sept. 7, 2012) (Isr.) (hereinafter: "State Comptroller Report").

³⁷ High profile criminal investigations were instigated against physicians working in Kaplan and Herzfeld hospitals. Allegedly these physicians conducted clinical trials on hundreds of elderly patients (most with a lack of cognitive abilities and many with severe dementia) with no therapeutic justification or informed consent. Some of the elderly patients died during the trials. However, despite the police recommendations to indict six physicians, the State Attorney's office decided in February 2011 not to prosecute. In view of the public outcry and condemnation by officials at the MOH, the MOH reported its intention to instigate disciplinary complaints against twenty one

reporting of clinical findings³⁸; while others were mentioned by the media in their engagement in illegal experiments conducted on soldiers.³⁹ These events led to highly publicized criminal investigations against Israeli physicians, a revision of the MOH guidelines and procedures, and ultimately several private⁴⁰ and government bills initiating new legislation. To date, no additional legislation has passed.

Against the backdrop of these events, another significant issue facing the Israeli COI framework has been identified: whether the Israeli public is aware and understands COI policies, concepts and procedures. Ethics deliberations and decisions are made behind closed doors, as well as clinical trial data, adverse events and disciplinary proceedings against investigators are not publicly available. There is no doubt that public trust in the integrity of medical research is crucial. Any scientific progress requires willing research participants and public support in order for research funding to be maintained. Scholars assert that historically the Israeli public has been a “weak healthcare stakeholder” arguably due to lack of information provided to it, and its generally passive interest in the health system.⁴¹

Although no quantitative data is available that accurately measures the level of the Israeli public understanding of their health system, intense media scrutiny emphasizing the inadequacy of the system tends to promulgate negative public opinion. Support for such negative public opinion can be found in Avinoam Reches’s (well known scholar and Head of the Ethics Department of the Israeli Medical Association) writings in which he indicates that: “even if the allegations

physicians involved in this case. To date, these proceedings have not yet been concluded. See Nativ Nachmani, Nisgar Tik Negeg Harofeem Sheashu Nissueem Bebnai Adam (the case against the doctors who conducted experiments on humans is closed), Maariv (nrg) (2011), available at <http://www.nrg.co.il/online/1/ART2/210/794.html> (last visited Sept. 7, 2012).

³⁸ In one case, Dr. Dicker, a well known Gynecologist, university professor and the head of the Helsinki committee, was convicted in 2009 for committing among other offenses a breach of trust. He was found guilty for submitting an article for publication to several U.S. medical journals based on fictitious clinical research. See CrimC (PT) 1424-07-09 *State of Israel v. Dov Dicker* (December 7 2009), Nevo Legal Database (by subscription) (Isr.).

³⁹ During the 1990s illegal experiments to test new ANTHRAX vaccine were conducted on Israeli Defense Forces soldiers. These illegal experiments allegedly had no scientific justifications and were administrated without adequate informed consent. For more information see Yossi Melman, Medical panel: Anthrax experiments on IDF soldiers were unjustified, Haaretz.com (2009) available at <http://www.haaretz.com/news/medical-panel-anthrax-experiments-on-idf-soldiers-were-unjustified-1.272877> (last visited Sept. 7, 2012).

⁴⁰ Private Bills are presented by a member of the Knesset or a group of Knesset members, as opposed to government bills which are presented by a minister member of the acting government.

⁴¹ Horev and Babad argue that the Israeli public gives higher priority to other issues such as national security and unemployment rather than issues related to the health system. See Tovia Horev & Yair M. Babad, Healthcare Reform Implementation: Stakeholders and their Roles— the Israeli Experience, Health Policy 71 (2005).

against the physicians would turn out to be false, the societal damage to the image of physicians and medicine in Israel is tremendous – and particularly threatens the future of clinical research in Israel.”⁴² [Translated from Hebrew] Moreover, as discussed in detail below several hospital professionals interviewed, including a couple chairs of the Helsinki committees, suggest that the public is indeed becoming wary, and further suggest that this lack of trust is the reason why fewer people are now willing to participate in clinical trials. One chair explicitly indicated that, as opposed to the past where subject recruitment was a fairly easy task, today the hospital has to terminate trials due to lack of participants.⁴³

1.2 Thesis Goals

This study examines the structure, standards and processes now in place in Israel addressing different levels of COI in medical research involving human participants. Specifically, it asks how the Israeli regime safeguards against the risks associated with competing interests in three thematic areas: individual investigator; members of the research review and approval process; and research institutions. Contrary to a rich, reliable and relevant literature regarding COI in the U.S. and Canada⁴⁴, there is very limited information and scholarly material on the Israeli biomedical research review and approval processes. There have been only a few legal cases for trial-related injuries, and as mentioned, scant information is available to the general public. Hence, this study attempts to accumulate vital empirical data that are otherwise unavailable to the public, in order to evaluate how the Israeli regime responds to COI issues in medical research. Particularly, this study builds upon the U.S. Institute of Medicine’s (IOM) report’s framework for evaluating the current Israeli COI policies and practices.⁴⁵ Based on the IOM

⁴² See Avinoam Reches, Introduction in Israeli Medical Association: The Ethical Department and Legal Department, Clinical Trials, at 3-4 (2006) (Isr.) The position paper is available at http://ima.org.il/ima/FormStorage/Type1/clinical_research.pdf (last visited Sept. 7, 2012).

⁴³ Interview with hospital 6 official, in Jerusalem, Israel (September 16th, 2010).

⁴⁴ For information regarding the Canadian approach to COI and the industry ties with researchers/research institutions see L. Ferris & D. Naylor, Promoting Integrity in Industry-Sponsored Clinical Drug Trials: Conflict of Interest for Canadian Academic Health Sciences Centers in Law & Ethics in Biomedical Research: Regulations, Conflict of Interest, and Liability 95-131 (Trodu Lemmens & D. Waring ed. Uni. of Toronto 2006).

⁴⁵ The IOM report was written in accordance with the National Research Council’s Report Review Committee to provide upfront and critical recommendations to assist institutions in their decision-making processes addressing COI issues and policies. See IOM report *supra* note 32.

report's standard, elements of transparency⁴⁶ and accountability⁴⁷ under the Israeli regime are tested and analyzed.

In evaluating Israel's current regulatory framework, it is instructive to look at the U.S. biomedical regulatory regime, focusing on its definitions and mechanisms to address similar COI issues. Although the U.S. and Israel are culturally and economically different, the former's model was best suited for a comparative analysis due to the following crucial factors. First, the U.S. system created the notion of institutional ethics committees and has rich experience with regard to ethics evaluations and COI issues. There is much material to draw from, including surveys, statistical analyses, and scholarly articles.

Second, Israel and the U.S. collaborate intensely on biotech innovation. Israel's life science industry exported six billion USD of products and services in 2009, of which 71 percent of sales were made in the U.S.⁴⁸ In addition, many Israeli physicians and researchers are trained via fellowships in the U.S.⁴⁹, and most of Israel's medical policies are aligned with those of the U.S. Thus, it is in Israel's best interest to comply with U.S. regulations in order to further enrich this collaboration between the countries.

Third, Dr. Matthew Tarosky, FDA Deputy Director in the Division of Bioresearch Monitoring Office of Compliance, stated in a 9/2009 interview that the U.S. FDA is planning to open a Middle East office, most likely in Israel.⁵⁰ The reason cited was because Israel is known for its considerable innovation in biotechnology and medical equipment.⁵¹ Hence, a comparative analysis may also assist in understanding both countries' regulatory policies for the purpose of

⁴⁶ Evaluating whether the COI policy's is accessible and comprehensible to the relevant institutions and individuals. *Id.* at 58

⁴⁷ Reviewing whether the COI policy identifies the relevant stakeholders responsible for monitoring, enforcing and revising it. *Id.* at 59.

⁴⁸ Christina Kakaflikas, Israel Investment Attraction Program, Report to Economic Development Committee (2011) available at <http://www.markham.ca/markham/ccbs/indexfile/Agendas/2011/Development%20Services/pl110308/Israel%20Investment%20Attraction%20March%208%202011.pdf> (last visited Sept. 7, 2012).

⁴⁹ Ahuva Koren, Benefits of Conducting Clinical Trials in Israel for Multinational Life Science Companies. *J. Biolaw & Bus.*, Vol. 10, No. 1, 2007.

⁵⁰ Paz Vaysman, FDA to open ME office - probably in Israel, *Haaretz*, September 11, 2009, available at <http://www.haaretz.com/hasen/spages/1113611.html> (last visited Sept. 7, 2012).

⁵¹ *Id.*

harmonization required for efficient and smoother acceptance of Israeli- based clinical data by the FDA.

Finally, both Israel and the U.S. adhere to similar ethical principles and similar regulatory frameworks for approval and oversight. Like the U.S. FDA, the Israeli regulatory regime explicitly acknowledges and adopts the provisions of the Good Clinical Practice Guidelines (GCP) issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).⁵² Notably these Guidelines do not address COI circumstances.

1.3 Research Questions

This thesis examines the processes and practices under the Israeli regime with regard to the protection against the risks associated with COI in biomedical research. Using a transformative strategy design, this thesis first asks an *inductive question*:

(1) How does the Israeli regime safeguard against the risks associated with COI in human participant biomedical research?

Subsidiary questions for this topic include the following:

- a) Who are the relevant stakeholders involved in the research approval and oversight under the Israeli regime?
- b) What are the conflicting interests involved in conducting clinical trials with human subject participants in Israel? What are the risks associated with COI in biomedical research involving human participants?
- c) How do the current Israeli biomedical regulations, policies, processes and practices protect against the risks associated with COI? For evaluating the current Israeli COI policies and practices the elements of transparency and accountability will be analyzed.

⁵² The main goal for the GCP standards was to harmonize the drug approval/registration processes among the U.S., E.U. and Japan in order to minimize redundant duplication of testing and other requirements for product registrations by these countries. By this, any unnecessary delay for product registration in these countries would likely be avoided, and the availability of new therapeutics would increase. A copy of the ICH Good Clinical Practice Guidelines E6(R1) from June, 1996, is available at <http://www.ich.org/LOB/media/MEDIA482.pdf> (last visited Sept. 7, 2012).

Then this thesis poses a *comparative question*: How does the U.S. biomedical regime addresses similar COI issues?

It asks:

- d) What are the regulatory and/or institutional arrangements in place under the U.S. scheme to address similar COI issues?

Finally and based on the comparative analysis, this thesis addresses a *transformative question*: What changes to the current Israeli policy and practices will best foster transparency and accountability to better safeguard against COI in biomedical human participant research?

1.4 Thesis Significance

This research is the first empirical study of the regulatory and institutional application of safeguards against COI in biomedical research under the Israeli regulatory scheme. It will contribute to the academic grasp of the importance of public governance through the lens of practical principles of research ethics. Ethically conducted research is an essential safeguard of moral and social values, such as protection of the validity of scientific research and safeguarding human health and safety. The protection for human participants' health and unbiased research against potential exploitation is and should be regarded as a global concern. There is thus a strong need for solid research, clear thinking and public discourse about this topic.

The analysis has at its premise the fact that the protection of human subjects and the preservation of research integrity within the context of medical research must evolve in step with the changing world of innovation and creative technologies. Studying Israel's approach and practices, and learning from the U.S. model, will offer a paradigm for the continuous improvement of practices that meet the ongoing challenges facing all countries. This study will highlight the importance of securing legitimate standards not only for biomedical investigators and medical institutions, but also for the welfare of the general public and those who contribute to scientific inquiry as clinical trial subjects.

1.5 Methodology

This thesis uses a pragmatic approach⁵³ to explore public governance processes and practices through the lens of contemporary bioethics. To answer the research questions described previously, a qualitative method was used to collect and analyze data. Such a method is well suited to situations characterized by limited information⁵⁴: indeed, in Israel there is limited research and scholarly material related to COI within the context of biomedical research. Because COI literature is lacking, this thesis has an important comprehensive inductive phase designed to provide crucial understanding on COI processes and practices under the Israeli biomedical regime.

As discussed below, data for this research was collected from document reviews (described below); and open ended interviews with three groups of officials discussed in detail below conducted between August, September 2010 and May 2011:

Reviews of Published Documents: Database and library review was conducted in order to have a baseline understanding of Israel and U.S.'s clinical trial regulatory framework responding to various COI issues. Understanding these regulatory frameworks was designed to advance the question of whether the Israeli framework for resolving potential COIs are adequate responses to the influence of commercial incentives and values. The comprehensive material reviewed for this research included: legislation, government's reports and policymaking documents, court cases, hospitals policies and guidelines, scholarly material and information posted online in several Israeli hospitals' websites. These documentations were collected from libraries, hospitals, and government agencies. The documents were derived from research conducted at the University of Washington libraries, and several universities in Israel, including the Hebrew University in Jerusalem, Tel Aviv University and Bar-Ilan University. In addition, other data were obtained from hospital officials, hospitals' websites, government officials, pending legislation, two national newspapers' online archives (Ynet-news and Haaretz), and Nevo (Israel's largest legal database containing legislation, court cases and legal scholarship).

⁵³ See John W. Creswell, *Research Design: Qualitative, Quantitative and Mixed Methods Approaches*, 11-12 (2nd ed. 2003). Creswell argues that the essence of the pragmatic approach in social science research focuses on identifying the problem followed by pluralistic inquiry to generate knowledge about the problem.

⁵⁴ Creswell indicates that qualitative research in its essence is an exploratory process, best used in circumstances where little research has been previously conducted. See *Id.*

In-depth, Open-ended Interviews: Qualitative open ended interviews were conducted in order to obtain the descriptive data to answer the inductive question and amplify information derived from the abovementioned document review. The purposive sampling frame used included key stakeholders in the ethical evaluations and regulatory compliance and oversight of research involving human participants in Israel. This sample included three groups of key officials at: (1) the MOH, (2) the National Ethics Committee and (3) hospital officials working in seven general hospitals.

The open ended interview methodology was selected for several reasons. First, interviewees can offer facts and perspectives that otherwise would not be known by reliance on written materials. When conducting pragmatic research, the best way to produce knowledge for the current problem is to investigate daily social practices through the work of relevant people utilizing the system⁵⁵ as well as through historical, political and social contexts.

Second, ethical review and oversight practices and experiences regarding COI issues cannot be found solely by performing document reviews. Institutional ethics committees, government advisory committees or the MOH's minutes and reports are not published. Also, other than instructions to review contractual agreements with commercial companies or COI screening rules for government advisors, the Israeli regulations do not provide definitions of COI or standards to eliminate or manage COI once identified. Hence, MOH and the institutions are left to provide their own internal guidelines and procedures to ensure compliance with the regulations. However, these internal guidelines and policies are not published online. Therefore, using open-ended interviews with relevant stakeholders provides otherwise unavailable information.

Since all the research participants are government officials or professionals working in hospitals, permission and support was obtained from the Director General of the MOH or the director of each organization to allow these professionals to participate in this study. Following the

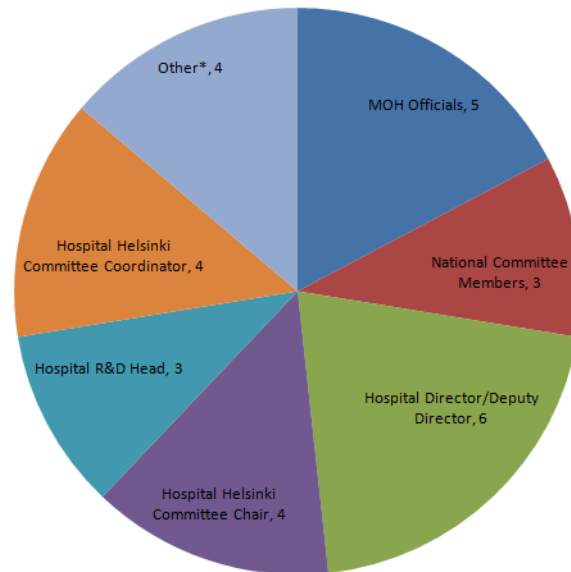
⁵⁵ For more information about the principles of the pragmatic researcher, see Jörg Friedrichsa & Friedrich Kratochwil, *On Acting and Knowing: How Pragmatism Can Advance International Relations Research and Methodology*, *International Organization* 63, 701–31 (2009).

directors' approval, an email of introduction was sent to all the research participants explaining the focus of this study.

A total of thirty one interviewees within these three groups of officials were approached directly via email or telephone and invited to participate in the study. Twenty nine agreed to participate, two did not respond (one of whom apparently was abroad at the time the emails and telephones were made), making a response rate of more than ninety three percent (29/31). A total of twenty nine interviews were conducted, twenty four interviews were conducted in person on a one-on-one basis, two interviews were conducted with two interviewees at the same time due to limited time and at the request of the interviewees, and one interview was conducted over the phone. All interviewees were asked to articulate their perspectives and experiences in the following two thematic areas: definition and identification of COI, and consequences of identified COI. To control for interviewees' potential bias and strengthen internal validity of this research, the goal was to interview several professionals from each group.

Of the twenty nine interviewees, five interviewees were from the Israeli MOH: including the Director-General of the MOH, a legal advisor, officials working at the Pharmaceutical Administration of the MOH (a government agency, similar to the FDA, responsible for monitoring and oversight of clinical trials in Israel), and a representative of the MOH's 'Committee for Contracts with Commercial Companies'. Three interviewees were members of the National Ethics Committee.

The remaining twenty interviewees consisted of hospital professionals working in seven different general hospitals. The interviewees consisted of: five hospital directors or vice directors (all physicians); four Helsinki committee chairs; three heads of hospital research and development (R&D) departments; four Helsinki committee coordinators; one hospital management representative and one physician member of the Helsinki committee; one hospital lawyer and; one member of the hospital's audit panel. Lastly, an interview was conducted with a member of the Israeli Medical Association (IMA). Figure 1.1 below shows the distribution of the different interviewees and their roles.



*Other: 1 Helsinki hospital committee member; 1 audit panel member; 1 lawyer; 1 member of the IMA

Figure 1.1: Distribution of Interviewees

- The purposive sample of hospital officials consisted of professionals working at seven different general hospitals⁵⁶ in the three major regions in Israel: five large institutions in the central region of Israel; one general hospital in the northern region, and one general hospital in the southern region. Of Israel's forty-five general hospitals operating in Israel, these seven are recognized as multi-district hospitals with the greatest concentration and variety of research activities.⁵⁷
- Of the seven hospitals chosen for the purpose of this study, six are either government or owned by Clalit Health Services⁵⁸, and one is owned by a non-profit organization. Together these seven hospitals conduct the vast majority of clinical trials and they also contain the highest number of hospital beds in Israel.⁵⁹

⁵⁶ The seven general hospitals are: The Hadassah Medical Organization, the Chaim Seba Medical Center, the Rabin Medical Center, the Tel Aviv Sourasky Medical Center, the Soroka University Medical Center, the Rambam Medical Center and Assaf Harofeh Medical Center. Each one has an operating Helsinki Committee, with member/chair names published on each medical website.

⁵⁷ See Bruce Rosen et al., World Health Organization, the European Observatory on Health Care Systems, Health Care Systems in Transition: Israel (Sarah Thompson & Elias Mossialos eds. 2003),

⁵⁸ Clalit Health Services is a non-profit health plan organization, similar to the U.S. HMOs, which operated its own network of hospitals and healthcare professionals. For more information see Clalit's website available at http://www.clalit-global.co.il/en/_the_story_of_clalit_health_services.html (last visited Sept. 7, 2012).

⁵⁹ According to the Ministry of Health statistics report from 2008, only 25 percent of the total medical institutions which operate in Israel have more than 200 hospitalization beds, with the largest being Chaim Seba Medical Center

- In brief, the following variables remain consistent in all the hospitals selected for the purposive sampling: regulated entities, multi-district general hospitals, conducts clinical trials, conducts a variety of research activities, responsible for ethical and regulatory compliance, oversight and monitoring by the MOH, required MOH reporting of number of clinical trials and adverse events, MOH approved ethics committees, use the MOH clinical trials forms, and conduct trials sponsored by private industry.

In order to obtain information regarding the processes and practices of the current system, the goal of the interview phase was to interview hospital officials conducting most of the clinical trials in Israel. Given the lack of publically available reports and institutional ethics committee minutes, these interviews offer one of the few avenues for obtaining crucial information about current practices and procedures. The focus of this study is to identify the Israeli regulatory procedures, policies and practices relating to COI issues, and not to evaluate the specific individuals involved in the processes. Thus the participants' identities are not important to the purpose of this study.

Notably, the purposive sample of hospital officials did not include officials working in all forty-five general hospitals operating in Israel, or hospitals that are privately owned. Also not included in the sample are small specialized medical institutions (in Israel they mainly include geriatric institutions and nursing homes), or other non medical hospital venues. Thus, there is no way to ascertain whether the policies and practices described by the sampled hospital officials is representative of all hospitals or other venues conducting clinical trials in Israel. In addition, in view of the non-random nature of the purposive sampling method used in this study, the findings in this research may not necessarily apply to the entire research community.

1.6 Thesis Organization

This thesis contains eight chapters. Chapter 2 explores the evolution of COI framework in its broad public context under the Israeli scheme, and discusses this framework's application in the context of biomedical research. The broad political context of COI provides the baseline for

in Ramat Gan with more than 1,400 beds. For more information about the medical institutions in Israel, please see Ministry of Health, medical institutions statistics report 2008 (Isr.) available at <http://www.old.health.gov.il/pages/default.asp?maincat=2&catId=587&PageId=4452> (last visited Sept. 7, 2012).

understanding the conceptual analysis of various COI issues under the Israeli scheme. Such analysis clarifies the important elements, definitions, and mechanisms related to COI issues in Israel. In the absence of clear regulatory guidance and empirical data, as in the case of COI issues in medical research in Israel, such analysis is required. In order to identify the characteristics of COI in Israeli biomedical research, this Chapter describes the current privatization forces and government initiatives increasing commercial incentives, followed by an overview of the development of regulatory oversight and monitoring mechanisms.

To understand how the current regulatory framework safeguards the risks associated with COI in Israel, Chapter 3 provides an overview of the structure, standards and processes of Israel's clinical research infrastructure. The comprehensive study of the regulatory infrastructure highlights the central role the medical institutions, particularly the Helsinki Committees, and the MOH play in safeguarding both the rights of human participants and the scientific validity of the research. Explicitly, the regulatory mechanism imposes upon the hospitals and the MOH the responsibility to identify and manage COI situations arising from the financial or contractual relationships between trial sponsors and investigators. Furthermore, the scheme also imposes a COI screening procedure to determine eligibility of government advisors used by the MOH for scientific and ethical input in the review of new clinical trial applications.

The discussion of these regulatory mechanisms in Chapter 3 serves as a theoretical benchmark for the analysis in chapters 4-6 regarding the practical interpretation and implementation of these mechanisms. Based on the literature review, each of the three chapters discusses a level of the research enterprise in which potential COI may affect the ethical conduct of medical research: the individual investigator level, the level of research reviewer, and the research institution level.

Chapter 4 explores issues of COI ascribed to the individual investigator conducting clinical trials in Israel. It is designed to evaluate whether the current regulatory framework and practices are adequately responding to the risks associated with investigator's COI in Israel. In order to evaluate that, this chapter employs two levels of analysis: conceptual and practical. The conceptual analysis describes the tension between on the one side the significant control clinical investigators have over the conduct of the clinical trial, and on the other side the entrepreneurial nature of contemporary medical research. Such tension creates concerns for COI, and asks

whether personal conflicting interests can undermine investigator's ethical and scientific responsibilities. This chapter further explores the significant studies published worldwide suggesting that the increasing collaboration with industry has in fact impacted research findings and publications, raising many concerns regarding the validity and objectivity of industry sponsored biomedical research, as well as legal or ethical concerns for individual researchers' misconduct and bias.

The practical analysis in Chapter 4 portrays the rules and processes in place to address COI at the investigator level. The analysis begins by demonstrating how concerns about investigator financial COI were explicitly addressed by the Israeli regulators through affiliation disclosure requirements and institutional and governmental review processes. This Chapter argues that these regulatory mechanisms lack definitions and standards for making COI judgments. It also argues that these mechanisms address only partial COI circumstances, resulting from sponsor-investigator affiliations and not other areas of COI concerns.

Chapter 4 then proceeds to discuss the information obtained from the interviews conducted with government officials and hospital representatives in charge of the COI review process.

Substantial variations were found among the interviewed officials with regard to the interpretation and implementation of the regulatory COI principles. The critique of Chapter 4 centers on the practical analysis of the implementation approaches to investigator COI in Israel, showing how these approaches raise a number of research governance practices issues. The following are among the critiques advanced in this chapter: the COI regulatory provision lacks standardized objectives and responsibilities, thus failing to reflect the Israeli scheme's stand on researcher COI; hospitals are implementing limited sources for financial COI assessment; and the current regulatory anomaly of imposing COI review and approval processes only on certain medical institutions.

Chapter 5 explores issues of COI ascribed to institutional ethics committees and government advisory committees who are assigned to ensure regulatory and ethical compliance in clinical trials in Israel. Similar to Chapter 4, this chapter is designed to evaluate whether the current regulatory framework and practices are adequately responding to the COI of the stakeholders responsible for ethical review in clinical research in Israel. This chapter also incorporates two

levels of analysis: conceptual and practical. The conceptual analysis, explores the Israeli regulatory model directed at the protection of the primary goals of clinical research by virtue of independent review and oversight mechanisms. These regulatory review and oversight responsibilities are mainly bestowed upon the institutional Helsinki Committee and/or the officials at the MOH. It demonstrates how the entrepreneurial nature of biomedical research, and the associations between the research reviewers and sponsors, creates several COI issues which challenge the core design of safeguards. The main concern centers on whether the increasing commercial sponsorship and growing financial incentives for reviewers and/or their institutions may have or be perceived to have impact on the reviewers' impartiality. As discussed in this chapter, in Israel, concerns have arisen as to whether this ethics review system is well-equipped to safeguard the primary goals of human research.

The practical analysis in this chapter describes how the Israeli regulatory framework distinguishes between the different actors involved in the research review process. While the various government advisory committees are governed by specific COI disclosure and management requirements, the institutional ethics reviewers are left to develop their own internal policies on COI related to their members. Chapter 5 then proceeds to discuss the information obtained from the interviews conducted with hospital representatives, members of the government advisory committee (the National Ethics Committee) and government officials to understand the processes and policies responding to reviewers COI. Overall, the interview data supports a conflict avoidance policy, where the reviewer-PI recuses him or herself from the discussion and decision-making process. Nevertheless, variations were found between institutional reviewers and government advisor reviewers with regard to the scope and definition of COI when other possible interests are involved.

The critique of Chapter 5 centers on the practical analysis of the implementation approaches to research reviewers' level in Israel. The following are among the critiques advanced in this chapter: the "Shared Pool Dilemma" raising tension between impartiality and competence, which increases the challenges for recruiting members to government advisory committees; the "disclosure deficiency" problem makes it difficult to interpret disclosed COI information under the current provisions; and the lack of regulatory COI provision for the institutional actors,

creates inconsistencies in interpretation and implementation, as well as narrow application of the hospital internal COI policies.

Chapter 6 explores issues relating to COI ascribed to institutions conducting medical research involving human participants. Similar to Chapters 4 and 5, this chapter applies two levels of analysis: conceptual and practical. The conceptual analysis discusses information about the Israeli hospitals conducting clinical research, and continues to focus on the framework of the largely institutional paradigm for approval and monitoring of clinical trials conducted at their premises. It then explores various worldwide studies suggesting institutions' entrepreneurial interests create financial COI, thereby calling into question the current self-policing strategy. The main concern is that potential biases within institutional decision-making practices and processes will jeopardize the health of research subjects, research integrity, and public trust.

The practical analysis shows that, unlike investigators and government advisors, the regulatory scheme does not provide mechanisms to address institutional COI. In fact, in some respect the regulatory provisions might intensify these institutional conflicts. Then the analysis focuses on the data obtained from interviews conducted with hospital professionals and officials at the MOH, to discuss how the institutions and the MOH are dealing with COI at the institutional level. Despite the absence of regulatory provisions, the interview phase suggests that some hospitals were addressing these conflicts applicable to financial interests held at their institution. Nevertheless, wide inconsistency was found in the measures taken at hospitals to respond to institutional COI.

The critique of Chapter 6 centers on the practical analysis of the implementation approaches to institutional COI in Israel, showing how these approaches raise a number of research governance practices issues. The following are among the critiques advanced in this chapter: rather than restricting clinical trial approval mechanisms to scientific and ethical considerations, the current regulatory regime appears to ensure joint assessment of factors related to ethics and profit; some hospitals lacked organizational barriers separating the responsibility for oversight of human participants' studies from the responsibility for institutional investment endeavors and technology transfer program; and government created hybridized research institutions with

profound financial incentives call into question the current regulatory and organizational framework and infrastructure and its ability to deal with potential institutional COI.

In light of the critiques discussed in Chapters 4-6 with regard to the Israeli COI regulatory regime, Chapter 7 explores the U.S. model and how it attends to similar COI challenges. The reference to the U.S. COI model only serves the purpose for comparative analysis and policy recommendations for the Israeli system. The comparative review of the U.S. regime explored in this chapter parallels the analysis of three thematic areas of potential conflicts discussed in Chapters 4-6: researcher; research reviewer; and institutional. It delves into the underlining current U.S. regulations, policies and guidance addressing COI related challenges found under the Israeli regime with respect to all the three thematic areas. Important differences between the two regulatory schemes' mechanisms are highlighted and analyzed. Following the review of the U.S. model, the chapter proceeds to confer the issue found in the Israeli regime related to the three levels of potential COI.

Based on the comparative analysis and the review of the current issues, this chapter makes policy proposals for reform. The proposed recommendations discussed in this chapter, aim to promote transparency and accountability to enhance scrutiny and uniformity to the Israeli biomedical scheme. Consistent with such objectives, these policy recommendations include key elements of COI disclosure applicable to all stakeholders involved in human participants' research, as well as clear definitions, standards and a structural basis for identifying and evaluating COI circumstances. It further emphasizes that any consideration for policy recommendation necessitates considerable discussion among scholars, scientists, government officials and the public to best foster a thorough and consistent governance framework for COI issues in the biomedical research arena in Israel.

Chapter 8 summarizes findings and concludes the discussion.

CHAPTER 2: Conflict of Interest in Israel: Public Discourse and Biomedical Research

“In other studies you go as far as others have gone before you, and there is nothing more to know, but in scientific pursuit there is continual food for discovery and wonder.” [Mary Shelly, Frankenstein]⁶⁰

In four sections, this chapter seeks to explore the evolution of COI framework in its broad public context under the Israeli scheme, and discusses this framework’s application in the context of biomedical research. The broad political context of COI, discussed in section 2.1, provides the baseline for understanding the conceptual analysis of various COI issues under the Israeli scheme. Such analysis clarifies the important elements, definitions, and mechanisms related to COI issues in Israel. In the absence of clear regulatory guidance and empirical data, as in the case of COI issues in medical research in Israel, such analysis is required. In order to identify the characteristics of COI in Israeli biomedical research, section 2.2 describes the current privatization forces and government initiatives increasing commercial incentives for research institutions, followed by an overview of the development of regulatory oversight and monitoring mechanisms. Such analysis clarifies the entrepreneurial characteristics of the biomedical research in Israel creating COI issues, and explains the government’s efforts through regulatory mechanisms to address these issues. Section 2.3 provides crucial definitions, description of relevant risks and the different levels of COI ascribed to biomedical research involving human participants, which serves as a theoretical benchmark for this study. Section 2.4 summarizes the key conclusions from the foregoing analysis.

2.1 COI Framework – The Israeli COI Doctrine in Public Discourse

This section discusses the evolution of COI in Israel in its broad public context. The discussion of the existing Israeli COI framework and how it applies to less traditional forms of public service is required, in order to understand the theoretical classification of COI issues under the Israeli scheme. These conceptual classification of COI issues specifically relating to the Israeli biomedical research are absent, as there are scant empirical data and scholarly material on the

⁶⁰ Merry Shelly, Frankenstein, Penguin Book Ltd. 54 (1992).

topic. Thus, providing an overview of COI under the Israeli regime will help to clarify some of the important elements, definitions and mechanisms addressing COI issues. Building on the Israeli conceptual framework of COI, sections 2.2 and 2.3 discuss the unique case of COI within the context of biomedical research.

The discussion in the next section seeks to demonstrate the broad interpretation and implementation of the COI doctrine in the public official context under Israeli judicial review and by other government officials such as the State Comptroller and Attorney General.

2.1.1 The Origins of COI – From Past to the Present

COI as a basis for public and political discourse is certainly not a new matter. The concept of COI originated with the notions of unacceptable bribery, judges' decision-making processes, and other private or familial COI. One of the earliest laws found in this matter is the Code of Hammurabi in Babylonia during the eighteenth century B.C, which punishes corrupt judges who alter their decisions.⁶¹ In ancient Athens, scholars argue that Plato demonstrates concern about COI in his classic, *Republic* by calling for the elimination of nepotism COI as part of his "ideal" republic.⁶² Further, in medieval times there were important discussions on the practices of judges receiving gifts from litigants.⁶³

Traces of early thinking about COI can also be found in the Jewish law in the Talmudic Halacha script, for example, regarding arbitrators. Per the old script, arbitrators were required to be trustworthy, avoiding familial or other personal relations to the subject matter.⁶⁴ Such close relations with the subject matter were said to create COI circumstances which invalidated the arbitrator's decision. Back in Talmudic times, those who were working on behalf of the public

⁶¹ The Code of Hammurabi §5 as translated to English by King, L.W. is made available by the Avalon Project at Yale Law School, available at <http://avalon.law.yale.edu/ancient/hamframe.asp> (last visited Sept. 7, 2012).

⁶² See Stuart C. Gilman, Joshua Joseph & Cheryl L. Raven, Conflict of Interest: Balancing Appearances, Intentions and Values, (Ethics Resource Center 2002) available at <http://www.ethics.org/resource/conflicts-interest-balancing-appearances-intentions-and-values> (last visited Sept. 7, 2012).

⁶³ For interesting review of the relations between bribery, gifts and the practices of judges in the Medieval Church time please see R.H. Helmholz, Money and Judges in the Law of the Medieval Church, 8 U Chi L Sch Roundtable 309 (2001).

⁶⁴ In his article, Aviad Hacoen, provides a valuable historical perspective on COI under the ancient Jewish law and contemporary issues of COI in Israel today. See Aviad Hacoen, The Prohibition against Conflict of Interest in Jewish Law in Conflict of Interest in the Public Sphere: Law, Culture Ethics, and Politics 127-128 (Daphne Barak-Erez, Doron Navot & Mordechai Kremnitzer, ed. 2009). [Hebrew] (hereinafter: "COI in the public sphere")

were required to be loyal and to avoid bias.⁶⁵ The Jewish law originally conceptualized public officials as servants. Thus, similar to a servant who has to be loyal and honest to his master, the public servant has to work for the interests of the public they represent.⁶⁶

Contemporary political discourse focuses on COI as a crucial mechanism for identifying and combating corruption. Corruption made center stage in the 21st century due to modern forces such as globalization and privatization influencing many practices and governance arrangements in many countries. Western countries had been attempting to fight circumstances where public officials abuse their power for private gain, along with the constant need to promote and maintain the public's trust. The Organization for Economic Co-operation and Development (OECD), for example, issued guidelines for managing COI in public service, providing a comprehensive international benchmark to assist governments in evaluating their COI policies and practices. The OECD asserts that in order to develop a sound institutional, legal framework and good international practices, countries must clearly identify what constitutes COI and what forces create COI.⁶⁷

2.1.2 The Israeli COI Doctrine – Sources and Goals

In Israel COI doctrine is embedded in numerous fields governing public ethics. The basic concept of COI is indeed rooted in the old Jewish teaching that public servants, as their name indicates, should act in the best interest of the public they represent. However, the modern conceptualization of COI doctrine was shaped by British law.⁶⁸ According to British law, the COI doctrine was developed through the principle of the natural justice as the rule against bias.⁶⁹ The British law against bias was adopted in Palestine during the British mandate along with other common law rules. Upon the creation of Israel, this rule implicitly became part of the new state law. Early on, the Israeli Supreme Court in the classic case of *Shimmel* explicitly adopted

⁶⁵ *Id.* at 129.

⁶⁶ *Id.* at 129-131.

⁶⁷ Michael Marien, *Managing Conflict of Interest in the Public Service: OECD Guidelines and Country Experiences*, (Future Survey 2005).

⁶⁸ The Israeli legal system is based on the British Common Law as it reflects the Britain sovereignty in the area prior to its establishment in 1948.

⁶⁹ The Natural justice concept was originally created by the British common law and was imposed on government administration. It prohibits officials from deciding cases when they may be biased (*nemo iudex in re sua*); and provides the right to individual to be fairly heard (*audi alteram partem*). Breaching the rule against bias will result in holding the administrative action as ultra vires. This doctrine can be found in cases from the mid 1800s. For more information see William R. Wade & Christopher F. Forsyth, *Administrative Law* 448 (8th ed. 2000).

it.⁷⁰ The *Shimmel* case indicates that the rule against COI serves two important goals: framing public officials' decision-making process only in terms of practical considerations based on their work criteria, and maintaining public trust in the public system.⁷¹ The COI rule is derived from the public servant's loyalty and duty toward the public it represents.⁷² In a sense, public officials are trustees of public's prosperities and legal practices.⁷³

The Former Chief Judge of the Supreme Court, Haharon Barak (hereinafter: "**Barak**")⁷⁴, interprets the prohibition against COI rule broadly and explains it has two distinct goals: pragmatic and normative. The pragmatic perspective aims to prevent situations in which agents use their authority improperly. The normative perspective calls for making sure that public service is implemented systematically, responsibly along with appropriate public standing.⁷⁵ The Israeli courts attribute significant importance to the normative aspect and public trust element, which therefore requires extra caution when dealing with suspicious cases of COI.⁷⁶

2.1.3 Rule against COI - Scope

The rule against COI is fundamental in the Israeli public arena as well as in certain private law areas.⁷⁷ It can be explicitly stated in the law⁷⁸ or be part of ethical codes of conduct.⁷⁹ The COI doctrine applies to every individual serving as a public official, such as the President, Knesset members, ministers and municipal officials. All public officials carry with them the principles of

⁷⁰ H CJ 174/54 *Shimmel v. Rashut Mosmechet*, 9 PD 459, 462 [1955] (Isr.)

⁷¹ *Id.*

⁷² See Itzhak Zamir, Conflict of Interest in Public Service in Jewish Law in COI in the Public Sphere *supra* note 64 at 232-234.

⁷³ Sheldon Krinsky, The Ethical and Legal Foundations of Scientific Conflict of Interest in Law & Ethics in Biomedical Research: Regulation, Conflict of Interest & Liability, 66 (Trudo Lemmens & Duff R. Waring ed. Uni. of Toronto 2006).

⁷⁴ Between the years in Supreme Court office (from 1995 until his retirement in 2006), Barak had immense impact on the Israeli laws and judicial scrutiny. Even today, as a faculty in one of the law schools in Israel and as an active scholar, he continues to influence the courts.

⁷⁵ See Aharon Barak, The Prohibition against Conflicts of Interest in COI in the Public Sphere *supra* note 64 at 36-37.

⁷⁶ Yuval Feldman, The Psychology of Conflicts of Interest in Service in COI in the Public Sphere *supra* note 64 at 67.

⁷⁷ See Aharon Barak *supra* note 75 at 39.

⁷⁸ For example, Public Service (Restrictions after Retirement) Law 5729-1969 (Isr.) imposes a chilling period of a retired public official before pursuing related work.

⁷⁹ In Israel variety of professional organizations formulated code of practice standards addressing specific COI circumstances, such as code of conduct for nurses, judges, lawyers and teachers. The code of ethics for physicians issued by the Israeli Medical Association will be discussed later.

COI rule whenever they act within the capacity of their public work.⁸⁰ In essence, the COI doctrine follows the position and not the individual.⁸¹

The rule against COI was established by the judicial system as part of the common law as a universal standard. Thus, per Israeli common law, the COI doctrine governs even though in some cases no explicated law or ethical codes exist. The Israeli Supreme Court in the leading case *Siaat Halikud* emphasized that the COI rule governs irrespective of written law.⁸²

The Israeli law and court have broadly expanded the COI doctrine beyond public officials to all professional agents or trustees working within the private sector, such as lawyers, doctors and accountants, who as part of their work established fiduciary duty to act in the best interest of their clients and, patients. Notably, section 10 of the Israeli Medical Practitioners Ordinance⁸³ explicitly adopted the COI prohibition rule which prohibits licensed physicians from working in other jobs if such jobs will create circumstances of COI to their responsibilities as physicians.⁸⁴

2.1.4 Defining the COI Rule and Its Elements

Generally, the COI doctrine stipulates that any individual conducting administrative functions or fiduciary obligations should not be in COI situations.⁸⁵ Barak clarifies that such a prohibition rule is prophylactic. Namely, this doctrine is preventive in nature and will apply regardless if any decision was ever made or whether any damage occurred. From the goals of the rule against COI, Barak exerts the following central elements of the COI doctrine:

- a) Special relationships – these special relations exist between two or more individuals or organizations. They are characterized as trust relations. The special nature of the relations is the level of dependence between the parties and the control of one on the other's affairs.⁸⁶

⁸⁰ HCJ 5734/98 *Tzadok Azriel and others v. Israel Land Council Subcommittee*, 55(5) PD 859, 865 [1999] (Isr.).

⁸¹ See Zamir *supra* note 72.

⁸² HCJ 531/79 *Siaat Halikud in Petach Tikva Municipality v. Petach Tikva Municipality*, 34(2) PD 566, 573 [1980] (Isr.) In this case the court reviewed whether a member of the management committee within the municipality can also serve as the chair of the same municipality's audit committee.

⁸³ Medical Practitioners Ordinance [Amendment] Law 5736-1976 at §10 (Isr.).

⁸⁴ This Act does not provide any definition to what constitute COI.

⁸⁵ See Daphne Barak-Ereaz, Doron Navot, Mordechai Kremnitzer Introduction to COI in the Public Sphere *supra* note 64.

⁸⁶ See Barak *supra* note 75 at 31.

- b) Controlling the affairs of another – such control is mostly manifested by the power to decide in the affairs of another.⁸⁷
- c) Interests – conflicting interests can be: financial, monetary, emotional, sentimental, personal or institutional.⁸⁸ Such conflicted interests are broadly divided into two categories: tangible, which includes financial interests; intangible, which includes professional advancement, reputation and publications. Yitzhak Zamir, a well-known Israeli legal scholar, argues that having tangible interest creates a rebuttable assumption for COI which may bias decision or behavior, similar to other personal interests such as nepotism.⁸⁹

In addition to extensive implementation of rules against COI, the Israeli court's overall approach posits the linkage between the public officials (fiduciaries for the public) and the conflicting interests as stringent and minimalistic.⁹⁰ The court's approach is that basically any identified connection supports a determination that the official's decision was made in COI. The capacity of the COI doctrine is dynamic and it changes in accordance to the specific circumstances of the case.⁹¹

2.1.5 Assessing COI - Objective Standard

The judicial branch applies a broad objective standard.⁹² Namely, the primary aspect of the COI doctrine asserts that even merely an appearance of COI, as opposed to actual COI, will result in disqualifying such individuals from taking part in the decision or serving in that position. In the *Grossman* case, Judge Barak concludes that the official's own subjective beliefs as to whether or not COI circumstances had actually occurred, is irrelevant.⁹³ The standard is intended to broadly classify COI as situations where reasonable persons believe that decision-making judgment has been wrongly influenced, whether or not it actually has.⁹⁴ Yuval Feldman, an Israeli legal scholar and law faculty member, explains that the foregoing approach is based on the premise that justice

⁸⁷ *Id.* at 34.

⁸⁸ *Id.* at 36.

⁸⁹ See Zamir *supra* note 72 at 262.

⁹⁰ See Yuval Feldman *supra* note 76 at 67.

⁹¹ See Barak *supra* note 75 at 31.

⁹² See Feldman *supra* note 76 at 36.

⁹³ CrimA 884/80 *State of Israel v. Grossman*, 36(1) PD 405, 420 [1981] (Isr.).

⁹⁴ See Dennis F. Thompson *supra* note 34 at 292-293.

should not only be made but it should also be seen.⁹⁵ This approach, widely accepted by the courts, is aligned with the fundamental goal of the COI doctrine to protect the public trust.

The COI doctrine allows a focus on decision-making motives rather than understanding true motives behind decision-making or their consequences. The goal is to avoid the need to assess in retrospect the considerations used for the decision.⁹⁶ Also, leaving the conflicted individual to decide whether he or she was under COI circumstances is problematic, and “...is akin to leaving the fox to guard the henhouse.”⁹⁷

2.1.6 The Real Likelihood of COI vs. The Reasonable Concern of COI Standards

To date, the Israeli Supreme Court concurrently uses two allegedly different formulated standards for evaluating COI.⁹⁸ At first in the *Shimmel* case⁹⁹ the court adopted the British law standard of a “real likelihood”, in which the doctrine will apply if the facts of the specific case raise concerns to real likelihood of COI. Later, in the *Siaat Halikud* case¹⁰⁰, Barak employed the “reasonable concern” standard analyzing mainly outward appearance.

On the face of it, the reasonable concern is a more stringent standard since a real COI is not required but merely a reasonable perception of such. Arguably, against the public servant’s obligations not to be in COI situations, the public has the right to deal with officials whose management of their affairs is not subject to COI.¹⁰¹ Although the Israeli courts tend to apply the stringent standard more often¹⁰², the question of which is the adequate standard is still

⁹⁵ Yuval Feldman *supra* note 76 at 67. Also see HDJ 279/60 *Gil Hall Ltd. v. Yaari*, 15 PD 673, 676 [1961] (Isr.).

⁹⁶ See Barak-Erez Daphne, *Conflicting Interests and Conflict of Interest in Administrative Law in COI in the Public Sphere* *supra* note 64 at 217.

⁹⁷ See Daphne Barak-Erez et al. *supra* note 85 at x.

⁹⁸ These two standards were originally formulated by the British common law. In Israel these two standards were discussed in the opposite opinions by Judge Maltz versus Judge Alon in H CJ 244/86 *Ravivo v. Ben Tov Yechiel*, 42(3) PD 183 [1988] (Isr.).

⁹⁹ See *Shimmel* case *supra* note 70.

¹⁰⁰ See *Siaat Halikud* case *supra* note 82. The court adopted the classic *R v Sussex Justices, Ex parte McCarthy* ([1924] 1 KB 256, [1923] All ER 233) where Lord Hewart created the principle that the mere appearance of bias is sufficient to overturn a judicial decision.

¹⁰¹ Zamir *supra* note 72 at 228-230.

¹⁰² See Daphne Barak-Erez, *The Annual Book of the Israeli Law, 1992-1993* 223 (Israel Bar-Tel-Aviv District 1994) (Isr.)

unresolved.¹⁰³ Barak argues that no decision is required. He believes that the standard will be determined by the context. Thus, where trust issues are more prevalent, such as in the case of judges, the more stringent standard will apply. Whereas, for administrative officials, actions will probably be reviewed under the real likelihood of COI.¹⁰⁴

Some scholars believe that in practice there is no real difference between these two standards.¹⁰⁵ Arguably, both tests are elusive and ambiguous. Such ambiguity leaves a relatively wide range for judicial discretion.¹⁰⁶

2.1.7 Limitation – Normative Claim

As in other doctrines, COI is certainly not absolute. Applying the COI doctrine too broadly has its own price. Arguably, strongly banning COI circumstances might cause more damage than benefit. A valid concern raised is whether the legal and public struggle against COI has gone too far. In the *Pachima* case judge Strasberg-Cohen stated that the court should apply the COI doctrine cautiously in order not to deter honest, good and talented people from roles they are suitable for due to unrealistic concerns.¹⁰⁷ Such an approach frames the issue as the delicate tension between objectivity, goals, and competence. Considering all the possible self-interests driving the individual when making decisions, it is impossible to use a wide preventive instrument without undermining the selection of people who could carry out administrative roles.¹⁰⁸

In the *Shimon* case, the court asserted that this is a relatively small price to pay compared to the essential need to protect the public's trust in public services. The court, however, mentioned that this is a judgment call to be reviewed on a case by case basis.¹⁰⁹ Taking such concerns into

¹⁰³ Per Zamir the public's right for fair dealings with their affairs should be regarded as constitutional right. See *supra* note 72 at 230.

¹⁰⁴ See Barak *supra* note 75 at 35.

¹⁰⁵ In many cases, both tests can potentially lead to the same result. As the term 'likelihood' was given the meaning of possibility rather than probability, both tests became one. Obviously, if there was no real possibility of COI, no reasonable person would suspect it.

¹⁰⁶ Zamir *supra* note 72 at 257-261.

¹⁰⁷ CA 6983/94 *Pachima v. Perez*, 51(5) PD 829, 835 [1998] (Isr.), also see HCJ 1045/89 *Yaakov Daniel v. The Mayor of Kiryat Ata*, 44(3) PD 157 [1990] (Isr.).

¹⁰⁸ See Feldman *supra* note 76 at 100.

¹⁰⁹ See HCJ 595/89 *Moshe Shimon v. The Supervisor of the Ministry of Interior Southern District*, 44(1) PD 409, 414 [1990] (Isr.).

considerations, the question whether the particular case justifies the application of COI rule, will be determined by the particular nature of the conflicted interest, i.e. whether the interest is direct, indirect or speculative. As clarified by Barak: “one might ask: where the limit is set and when the conflict of interest chain of events will be stopped? My answer is simple: the chain will be disrupted in that link from which forward there will be no more objective concern for conflict of interest. The standard is not causal-factual but rather normative.”¹¹⁰ [Translated from Hebrew]

2.1.8 Consequences of COI – Criminal, Disciplinary, Civil and Administrative

As mentioned, the prohibition against COI rule can be explicitly stated in the law, be part of ethical codes of conduct or part of the judge-made common law as part of the natural justice doctrine. Briefly, breaching the COI rule might have several implications in various different levels depending on the source of the rule: criminal, ethical and administrative or contract.

Criminal Proceedings – there are general and specific punitive provisions.

Specific punitive provisions are included in various specific laws. For example, Civil Service (Limitations on Retirement) Law 1969, which impose a variety of limitations on public servants following their retirement.¹¹¹ Also, § 3 of the Civil Service (Gifts) Law 1979 states that if a public servant failed to disclose a present he or she received and to act in accordance with the provisions of the law, he or she will be fined.¹¹² This statute was explicitly extended not only over physicians working in government hospitals but also in other public hospitals. In addition, this Law includes in its definition of the term benefit or gift any gift received from manufacturer, importer or distributor of medical product (drugs, medical device etc).¹¹³ The Law aims to prevent the perception that the gift or benefit was given in order to create bias.

The Penal Code 1977 – Chapter 9 concerns destruction of public services and contains several criminal offenses based on the conceptual prohibition against COI. The most severe offense is

¹¹⁰ HCJ 202/90 *I.B.M. v. The Ministry of Justice and others*, 45(2) PD 265, 273 [1990] (Isr.).

¹¹¹ For example, the Law prohibits the retired public servant to work in a business that was under his/her review while they were in office, or to receive any benefits thereof. See Public Service (Restrictions after Retirement) Law 5729-1969 at §4 (Isr.).

¹¹² The fine will be three times the value of the gift/benefit.

¹¹³ The law excludes any low value and reasonable gift/benefit from the prohibition provision. See § 2(b) & §4 to the Public Service (Gifts) Law 5740-1979 (Isr.).

bribery.¹¹⁴ However, the court typically addresses circumstances of COI through the elusive offense of “deception and breach of trust” based on §284 of the Penal Code. Barak asserted that in order to apply the breach of trust offense, the state has to prove that the official was involved in a severe conduct violation with severe implications. These severe implications were interpreted to include fundamentally impeding the public’s trust in public officials, their integrity or the soundness of the public administration.¹¹⁵

In the *Shavess* case the court emphasized that there is a direct correlation between the position and the severity of the action. The higher the level of the position is the likelihood that the action will be regarded more severely.¹¹⁶ The court explained that the breach of trust offense is a crucial tool in the society’s fight against bias and inappropriate conduct. Per Barak, eliminating or narrowly imposing such offense will ultimately impede the public’s power to defend itself from those officials who abuse their authorities.¹¹⁷ Per Barak:

“The criminal sanction is aimed to ensure that fiduciary duty will remain, and the power of rule will not become the rule of power. We want to have in progressive Israeli society which is built on proper public administration, the rule of law, and interpersonal relations based on honesty, fairness and integrity. The criminal prohibition of the breach of trust was aimed to ensure these goals”.¹¹⁸ [Translated from Hebrew]

At the same time, strong criticism was raised in the literature alleging that the courts are excessively using the criminal proceedings as a tool to fight COI.¹¹⁹ Such opinion was raised by the descending Judge Tirkel in the *Grossman* case. Judge Tirkel asserted that the breach of trust offense is a borderline ethical offense, or namely “an ascetical defect”, and thus should not be regarded as criminal behavior.¹²⁰

¹¹⁴ §290 to the Penal Code 5738-1977 (Isr.) which impose up to 3 years in prison.

¹¹⁵ See Barak *supra* note 75 at 40.

¹¹⁶ See ADCrimA 1397/03 *the State of Israel v. Shavess*, 59(4) PD 385 [2004] (Isr.) in this case the former CEO of the prime minister office, Shimon Sheveass, was convicted for violating the breach of trust offense. While in office, Shevass promoted, through various actions, the affairs of his friends and business associates.

¹¹⁷ *Id.*

¹¹⁸ *Id.*

¹¹⁹ See *supra* note 109.

¹²⁰ See *Grossman* case *supra* note 93.

Disciplinary Proceedings – disciplinary proceedings can be instigated regardless of or in addition to a criminal conviction. A state employee, for example, taking an action in COI circumstances might be regarded as being guilty of inappropriate behavior under §17(c) of the State Service (Discipline) Law 5723-1963. Notably, physicians working for state owned hospitals, are state employees under the law, and thus are subject to these provisions. Violation of this law may trigger disciplinary proceedings against the employee in the State Employees Disciplinary Tribunal. The Disciplinary Tribunal and the Supreme Court consider state employee cases of bias promoting private interests very severely.¹²¹ The Tribunal is authorized to dismiss the employees from their job with no compensations or pension. Other actions may include warning or severe reprimand against the employee.¹²²

Disciplinary proceedings may also be instigated by a professional organization in relevant cases in accordance to a specific ethical code of conduct. Ethical codes of conduct primarily provide a framework for ethical decision-making in the conduct of professional work. The Israeli Medical Association (“IMA”), representing the vast majority of physicians in Israel, revised its physician’s code of ethics in 2009. This code of ethics is the profession’s ethical benchmark binding all physicians in Israel.¹²³ Briefly, the IMA code specifies that doctors and researchers should avoid being in COI circumstances, while they have to act in the best interest of their patients. This code also requires physician investigators to disclose any financial interest with industry and any other possible COI.¹²⁴ Failing to comply with the provisions of this ethical code, may cause the imposition of various sanctions on physicians including revoking the physician’s membership. In view of the prestige status of the IMA in Israel, and the benefits it provides to its members, such consequences can be harsh.

¹²¹ Judge Frokatcha discussed the severity of those who exploit their official power to promote the affairs of the people close to them, especially when the official is in fact senior monitoring and oversight officials. These public officials creating bias to promote their private agendas undermining the public’ trust in the municipal enforcement systems. The Judge asserted that unequivocal disciplinary proceedings are in order to help “clean up” the services from any corruption, and to rehabilitate the trust in the public systems. See AAM 9449/06 *Zazzon v. Jerusalem Municipality*, (October 22 2007), Nevo Legal Database (by subscription) (Isr.).

¹²² §25 of the State Service (Discipline) Law 5723-1963 [1963] (Isr.) provide a list of the possible actions against employee.

¹²³ Physicians, who failed to comply with the provisions of this code of ethics, might be subject to disciplinary proceedings which may result in cancellation of membership. IMA’s Code of Ethics from 2009 is available at <http://www.ima.org.il/MainSite/ViewCategory.aspx?CategoryId=3676> (last visited Sept. 7, 2012) (Isr.) (hereinafter the IMA Code of Ethics)

¹²⁴ See Chapter D.5 “The Physician and the Commercial companies”, *Id.*

Generally, however, ethical codes commonly suffer from lack of enforceability mechanisms. Zamir points out that specifically in Israel, principles of ethic are unsuccessful tool to combat COI, since the Israeli society prefers the protection of laws over the protection of ethics. This explains the rigorous active legalization of ethical norms, particularly those of COI provisions.¹²⁵ Per Zamir: “when an ethical norm becomes a legal rule, it is evident that the society failed to comply with its ethical norms appropriately. By virtue of legalizing of ethical norms, there is a risk of over legalizing behavioral norms. At the same time, this also means that the society acknowledges the importance and validity of such norms, and thus creates stronger ways to deter their breach. Such an “upgrade” was given to the COI rule”.¹²⁶ [Translated from Hebrew]

Civil Proceedings – the Supreme Court acknowledged the right to instigate certain civil proceedings against officials or fiduciaries who acted in COI. For example, the principal may have the right to sue their fiduciary through the provisions of the Trust Law.¹²⁷ Breaching the fiduciary duty may initiate different remedies according to the type of damage or benefit. Typically, they include restitution and pecuniary compensation.¹²⁸

Administrative actions – Officials or fiduciaries can be subject to administrative actions initiated by their supervisor based on the law and employment contract. The supervisor can also instigate civil proceedings against the employee acting in COI for breach of contract provisions.

2.1.9 COI Outcome and Remedies

The possible legal outcome and remedies for COI differ based on the nature of the action, interest, position and the governing law. Within the public official context, the COI outcomes vary and may include: transferring the matter to non-conflicted officials; abstention from taking part of the discussions, preparation and voting; involving other objective officials or representatives in the decision-making process; disclosure provisions; and disqualification. The

¹²⁵ See Zamir *supra* note 72 at 274-275.

¹²⁶ *Id.* at 277-279.

¹²⁷ Trustee relations can be invoked though a particular law or by a contract. See §2 to the Trust Law 5739-1979 (Isr.).

¹²⁸ *Id.* at §12 & 13.

court indicated that disqualifying officials from office should be considered as the last resort, taking into account the constitutional right of the freedom of occupation.¹²⁹

Can disclosure and acceptance by the subject neutralize the prohibited COI? Barak thinks that it does not. He asserts that disclosure or acceptance (by the fiduciaries) is irrelevant, since the pragmatic and normative goals of the COI doctrine are not met by merely disclosing or accepting COI.¹³⁰ Objecting to neutralizing prohibited personal COI by disclosure and acceptance can also be found in the old teaching of the Jewish Law.¹³¹ In terms of the validity of the action and decision made in COI, Barak holds the view the any decision made in COI is unreasonable.¹³² The court will first assess whether COI had indeed impacted the decision and action. If so, then the court will review which part of the decision and action was impacted and will invalidate that part only.¹³³

As COI has moved to the forefront in the fight against corruption, to the judicial scrutiny and legal frameworks other informal mechanisms were added to address COI within the public sector and to enable systematic public scrutiny.

2.1.10 State Comptroller and Attorney General

Both the Attorney General¹³⁴ and the State Comptroller are very influential figures in the fight against corruption, COI, and bias. The Attorney General publishes many binding guidelines for all state employees from time to time. The Attorney General guidance from 2006, for example, discusses the mechanism for current public officials or newly nominated officials to first seek the attorney General or its delegations' review and arrangement in a way that will address issues of

¹²⁹ The Basic Law: Freedom of Occupation 1994 §3 establishes that "Every Israel national or resident has the right to engage in any occupation, profession or trade." (Isr.)

¹³⁰ See Barak *supra* note 75 at 43.

¹³¹ See Hacoheh *supra* note 64 at 175.

¹³² See Barak *supra* note 75 at 41.

¹³³ HCJ 202/90 *I.B.M. v. The Ministry of Justice and others*, 45(2) PD 265, 273 [1990] (Isr.)

¹³⁴ The Attorney General is the head of the legal system of the executive government and the administrative agencies. Among the Attorney General responsibilities are the protection of the public's interest in the legal system. For more information about the Attorney General see the Ministry of Justice website available at <http://www.justice.gov.il/MOJHeb/YoezMespati/Odot.htm> (last visited Sept. 7, 2012) (Isr.).

COI.¹³⁵ This mechanism is aimed at proactively addressing any potential COI in advance; allowing the official a strong defense should allegations arise.

The State Comptroller, within the capacity to review the legality of all government agencies, also focused his efforts on revealing and reporting COI incidents. In a relatively high number of reports, the State Comptroller investigated and reported various incidents of COI, which led to high profile criminal investigations and trials. There is no doubt that both the State Comptroller and the Attorney General, both in retrospective and in proactive approaches, manage to prevent COI situations. They also allowed for the continuous public awareness and scrutiny through their published reports and investigations.

In sum, in Israel there is rigorous, active, judicial review of the ethical norms relating to COI doctrine. The abovementioned review suggests a very broad interpretation and implementation of COI under judicial analysis. Israeli courts have broadly encompassed within the protected COI doctrine any position with fiduciary obligations (public or private); any type of interest (private or institutional); under a very broad perception of appearance irrespective of actual COI. To the relatively broad judicial review, several other steps aimed to address various levels of COI at the administrative level, including the State Comptroller, Attorney General and other cooperation and representations statutory measures were added.

2.2 COI Doctrine – The Medical Research Case

2.2.1 Until 2004 – Hospital Officials Self-policing and Limited Oversight

Despite rigorous judicial and legislative scrutiny of public officials since statehood, public oversight of biomedical research was almost non-existent until 1980. Before 1980 no formal procedures for the application, review or approval of clinical trials existed. At the time, the approval and oversight of clinical trials in Israel was conducted solely at the MOH level by small

¹³⁵ See The Attorney General Guidance: Preparing Arrangements to Prevent COI in the Public Service, no. 1.555 (June 2006) (Isr.). The guidance states that the individual has the responsibility to avoid being in COI, as well as to report back to the Attorney General if the circumstances relating to COI have changed. This guidance is available on-line at <http://www.justice.gov.il/NR/rdonlyres/85C736FB-F8D3-494D-885E-2F92E392115F/12239/A11555.pdf> (last visited Sept. 7, 2012) (Isr.)

number of health professionals.¹³⁶ Due to the growing numbers of trial applications and the necessity to obtain regulatory approval in a timely manner, the Director General of the MOH enacted the Public Health Regulations in 1980. Generally, the Public Health Regulations imposed the review and approval of all clinical studies on human subjects conducted in hospitals in Israel on the following key stakeholders: (1) the medical institution's governing Helsinki Committee (Israel's medical institution ethics board)¹³⁷, its Director, and/or (2) the Director General of the MOH or its designees.¹³⁸ The Public Health Regulations also established the statutory advisory committee - the National Ethics Committee ("National Committee") - to assist the MOH with its review and approval mission. The Public Health Regulations explicitly adopted the Declaration of Helsinki¹³⁹ as the primary source for ethical guidelines.

In 1999, the Pharmaceutical Administration within the MOH published its Guidelines for Clinical Trials in Human Subjects ("Guidelines for Clinical Trials") which was later revised in 2006. These Public Health Regulations and Guidelines for Clinical Trials provide the regulatory framework governing the approval and oversight of clinical trials involving human subjects. For detailed information regarding Israel's clinical research infrastructure and processes please refer to Chapter 3.

Until the beginning of the new millennium, the integrity of physicians was assumed, hospitals were self-policing, and regulatory oversight and monitoring mechanisms were rarely enforced by the MOH.¹⁴⁰ The MOH's limited monitoring and oversight role during that time was well described by the then Director-General of the MOH, Prof. Gabriel Barbash, as quoted in a 1997 article.¹⁴¹ Barbash was asked about the MOH role in protecting the objectivity of trials funded by

¹³⁶ See Hannah Bilig, Clinical Trials in Israel, Pharmaceutical Administration, Ministry of Health (no date) available at www.old.health.gov.il/Download/pages/nisoiim_kliniim.doc (last visited Sept. 7, 2012) (Isr.).

¹³⁷ Israel's Helsinki Committees serve as the medical institution's administrative arm responsible for reviewing all research proposals within its facility to ensure regulatory compliance and protection of trial participants.

¹³⁸ See Public Health Regulations (Clinical Studies in Human Subjects), 1980, KT 4189, §§ 2 - 4. (Isr.) (hereinafter: the Public Health Regulations)

¹³⁹ See the Declaration of Helsinki *supra* note 33.

¹⁴⁰ Similarly, in the U.S. before the 1980s, the universities and their scientists were hardly under the radar, while no systematic public oversight was implemented. See Perry Molinoff, Conflict of Interest in American Universities in the Penn Center Guide to Bioethics 282-283 (Vardit Ravitsky, Autum Fiester & Arthur L. Caplan ed. 2009).

¹⁴¹ Sharit Rosenblum, Anachnu Shphane Hanisyunut Shel Haolam (We are the Genius Pigs of the World), Yedit Acharonot (March 3rd 1997) (Isr.) In her article Rosenblum describes Israel as a center for human experimentations for international pharmaceutical and medical devices companies. Rosenblum describes a dangerous situation in which the big companies are exploiting the population in Israel for their profit gain, while the hospitals conducting

commercial companies, he was quoted: “there are in the world some well known incidents of investigators who forged research findings; however medical research is based on trust. We do not have the resources and we are also not constructed to check each and every research study. If no one will actively blow the cover of a problematic trial, we will never know about it.”¹⁴²

[Translated from Hebrew]

2.2.2 Privatization Force – Increasing Commercial Incentives

Concurrently with the backdrop of scarce oversight and strong professional control in medical research, Israel has been undergoing a profound transformation of privatization.¹⁴³ Since the mid 1980s, in order to lower the budgetary deficit, the Israeli government has adopted and implemented a “free market” economic model aimed at reducing the government’s expenditure on social services, such as education and health,¹⁴⁴ and deregulating the barriers on publicly held institutions.¹⁴⁵ According to Daphne Barak-Erez, a well known Israeli legal scholar specializes in constitutional and administrative law, such transformation is attributed to strong U.S. political and cultural influences on the Israeli public which made the private-oriented economy model more appealing.¹⁴⁶

Thus, public non-for-profit hospitals including several owned by the government began operating and implementing business-like organizational schemes to maximize profits or to remain solvent.¹⁴⁷ These hospitals introduced private, patient-funded hospital services to generate income.¹⁴⁸ Another source for revenues was the public hospitals’ collaborations with

the trial generate millions of dollars every year. She also portray that practically there is no external oversight or monitoring of these trials.

¹⁴² *Id.*

¹⁴³ Israel’s economic model has been going a profound transitioning from government centralized system to privatization. This economic transitioning mirrors the political transformation from a socialist ideology at the beginning of statehood to free market ideology. See Daphne Barak-Erez, *Civil Right & Privatization in Israel Yearbook on Human Rights*, 205 Kluwer Law International (1999).

¹⁴⁴ See Dani Flic, *The Health Business Under Neo-Liberalism: The Israeli Case*, 25 *Critical Soc. Pol’y* 180 (2005).

¹⁴⁵ Dani Flic, *The Privatization of the Health Care System and its Commercialization* (2007), available at <http://www.ynet.co.il/articles/1,7340,L-3372021,00.html>, (last visited Sept. 7, 2012).

¹⁴⁶ See Barak-Erez Daphne, *Civil Right & Privatization in Israel* *supra* note 143 at 206.

¹⁴⁷ See Flic *supra* note 145.

¹⁴⁸ Such services allow patients to choose their specific surgeon or treating physicians, and to shorten the time for the operation. Such service requires an additional payment on top of the basic cap paid for hospital services. Israel Medical Association supports in providing private hospitals services within the all the public hospitals in Israel. They maintain that such private hospital services will better utilize the facilities and allow the hospitals to have revenue generating mechanism. See Tuvia Horev & Yair M. Babad, *supra* note 41.

the biomedical industry for fee administrating clinical trials on their behalf. The revenues generated by clinical trials from the industry contributed to the hospitals' operations including the ability to obtain advanced medical equipment.¹⁴⁹ As an example, during 2010 non-for-profit hospitals generated¹⁵⁰ 282 million NIS from administrating clinical trials for the industry.¹⁵¹

Within the profound privatization policy of the health system in Israel¹⁵², is the MOH plan to help government hospitals generating even more revenues from research.¹⁵³ Officially, to date the government retains all the intellectual rights to the research and discoveries developed within its owned hospitals. Based on this suggested plan, discussed in detail in Chapter 6, the government hospitals will be allowed to retain a portion of the patent rights of their new research discoveries fueled by public funding. The goal is to incentivize government hospitals to commercialize their scientific discoveries by allowing them the opportunity to generate patent related income.

Such policy is very similar to the goals of the U.S. Bayh-Dole act from 1980 (35 U.S.C. §200-212). This U.S. act was also designed to incentivize public universities to commercialize their discoveries¹⁵⁴ and, as mentioned above indeed in recent years, academic institutions have increased technology transfer and flourished on their ties with industry. In a sense, such policy allows “public investment to turn into private wealth”.¹⁵⁵ The economic scholarship in the U.S. by and large supports domestic technology transfer policies arguing that such policies are

¹⁴⁹ L Hochman., A. Caspi, W. Blasi & V. Charlton, Conducting Clinical Trials in Israel Sponsors find a diverse population, good medical facilities, GCP-compliant investigators, and efficient regulatory processes in Israel, *Applied Clinical Trials* vol. 10 63 (2001).

¹⁵⁰ Money generated from clinical trials by the industry is streamed to the hospital research funds.

¹⁵¹ See The Marker report *supra* note 9.

¹⁵² Among the primary goals of the privatization process in the health system aims to eliminate or reduce the inherent COI of the MOH associated with its dual role of directly operating health services and regulating and policy making. The majority of analysts and investigatory committees over the years consider such dual role as one of the major flaws in the system. See D. Chinitz, *Israel's Health Policy Breakthrough: The Politics of Reform & the Reform of the Politics*, *Journal of health Politics, Policy & Law* 20 (1995).

¹⁵³ For the last few years hospitals have been lobbying for regulatory changes in order to seek ways to increase their revenues in view of the constant health funds pressure to lower their services rates. Tuvia Horev & Yair M. Babad *supra* note 41.

¹⁵⁴ The 1980s – 1990s area reflected the critical change in public policy in the U.S. pertaining to technology transfer and competitiveness. Barry Bozeman, *Technology Transfer & Public Policy: A Review of Research & Theory*, 29 *Research Policy* 627 (2000).

¹⁵⁵ See Krinsky *supra* note 73 at 67.

effective tools to promote national growth.¹⁵⁶ However, many critics argue this act also contributed to the erosion of trust of the U.S. public in the academic enterprise as universities and individual investigators were all of a sudden perceived as a profit driven entities.¹⁵⁷ Arguably, the commercial-oriented academic model is at odds with the academic ideals of freedom of information and objectivity. In the U.S., discussed in Chapter 7, the tensions between commercial interest and objectivity were addressed by disclosure and COI management mechanisms in public funding institutions.

The Israeli government's incentives policy may enable entrepreneurship opportunities to both hospitals and their scientists taking on an active role in the commercialization of their discoveries. It might also serve to produce significant and innovative scientific progress and health developments. At the same time, this initiative will also help to build closer collaboration between government hospitals and industry, promoting a competitive and entrepreneurial research enterprise. These widening financial opportunities raise issues of COI relating to the official or institution that owns it. This commercially-oriented policy can arguably bring to light the most critical tension between private and public interests. While the public interest paradigm focuses on maintaining open and free access to intellectual discoveries, the private interests seek to control and restrict access to information to maximize profit goals.¹⁵⁸ Such shift in policy, in the U.S. during the 1980s, has indeed contributed to the shift in focus regarding COI. As Lemmens describes, while historically the COI commentaries focused on the individual researcher conflicted interests, now attention has shifted to COI at the institution level.¹⁵⁹ These factors arguably exacerbate an inherent conflict between the interests of the hospitals conducting clinical trials and their legal and moral obligation to protect the trial participants and research objectivity.¹⁶⁰

¹⁵⁶ Barry Bozeman & Daniel Sarewitz, Public Values and Public Failure in U.S. Science Policy, *Science & Public Policy* 32, no. 2 (2005), 119-136.

¹⁵⁷ See Molinoff *supra* note 140 at 282-283.

¹⁵⁸ See Bouchard *supra* note 15.

¹⁵⁹ See Lemmens *supra* note 29 at 747.

¹⁶⁰ Other scholars expressed their ethical concern regarding the equitable distribution of the significant profits made from public funding. Per Bouchard, when the substantial profits were generated from public contribution, the regulatory system needs to ensure equitable sharing to the public to avoid exploitation. See Bouchard *supra* note 15.

Not only do hospitals collaborate with the private industry in clinical trials to generate profits, but also the scientists who work in public institutions are increasing their financial ties with the industry or seeking entrepreneurial opportunities from their new discoveries. In Israel, physicians working in government owned hospitals seeking to engage in private activities, requires the approval of the director of the relevant hospital, and will result in reducing his or her salary in five percent.¹⁶¹ Private-public investigators conducting medical research with entrepreneurship and/or financial ties with the industry, causes concerns for COI.

2.2.3 State Comptroller 2004 Report - Serious Legal and Ethical Deficiencies

Accompanying such increasing commercial incentives called for enhanced public scrutiny. It was not until the 2000s that the myth of physicians as selfless and objective scientists was shattered. A well-publicized report issued by the State Comptroller¹⁶² in 2004 brought to light serious ethical and legal violations (some of which involving COI issues) and have shaken the system. The adequacy of the current regulatory system has been publicly called into question. This high profile incriminating report highlighted serious ethical deficiencies with respect to prestigious medical institutions. The report specified several hospitals that conducted research in the years 2002-2004 with inadequate informed consent and/or therapeutic justification on elderly patients --allegedly causing death to participants. Further, conflicting roles among some of the Helsinki Committee members (institutional ethics committee) were found as some committee members approved protocols of their own studies; in many cases, these Committees were but ‘rubber stamps,’ approving all research applications with no oversight.¹⁶³ The Report also found that investigated hospitals failed to report to the MOH all the trials conducted within their premises as required by the Guidelines for Clinical Trials.¹⁶⁴ Lastly, the Report revealed that only a third of the trial related incidents of death to participants were reported to the MOH within 48 hours as required, in some cases the reports were issued several months later.

¹⁶¹ This is similar to France where public physicians can work outside the public hospitals under certain conditions, resulting in reducing their salary in twenty percent. However, contrary to France, in Israel there are no restrictions or caps on the private fee these public-private physicians can charge their patients. See Rodwin *supra* note 19 at 54.

¹⁶² The Israeli State Comptroller, usually a retired judge, is appointed by the President with the recommendation of the Israeli Parliament (the Knesset) and is responsible by law for reviewing, investigating and supervising government agencies’ and public institutions’ policies and operations. The State Comptroller’s findings are brought to the investigated bodies, the Knesset and the public. More information is available at <http://www.mevaker.gov.il/serve/site/english/index.asp> (last visited Sept. 7, 2012).

¹⁶³ The State Comptroller’s Report 55 (2004) *supra* note 36.

¹⁶⁴ At the time of the report, the MOH was informed of only 50 percent of the total trials conducted in the investigated hospitals and only 78 percent in 2003.

This damaging 2004 report led to high profile criminal investigations against physicians working in Kaplan and Herzfeld hospitals. Allegedly these physicians conducted clinical trials on hundreds of elderly patients (most with a lack of cognitive abilities and many with severe dementia) with no therapeutic justification or informed consent (“Kaplan-Herzfeld case”). Some of the elderly patients died during the trials, a fact which was never reported to the MOH. Important to this study, was the fact that the elderly trials were the basis for professional advancement for some of the physicians as well as publications in medical journals both locally and internationally.¹⁶⁵ However, despite the police recommendations to indict six physicians, in February 2011 the State Attorney’s office decided not to prosecute.¹⁶⁶ In view of the public outcry and condemnation by officials at the MOH, the MOH reported its intention to instigate disciplinary complaints against twenty one physicians involved in the Kaplan-Herzfeld case¹⁶⁷ which may result in revoking the physicians’ medical licenses.¹⁶⁸ To date, these proceedings have not yet been concluded, and it seems that the physicians are still practicing medicine.

2.2.4 The Aftermath – Strengthening Monitoring and Oversight Mechanisms

Following the publicity of the State Comptroller’s report, the processes and practices aimed at safeguarding against the risks associated with trials, particularly the risk to harm participants, came under increasing scrutiny. Numerous news reports describing upsetting conduct of physicians to vulnerable elderly geriatric patients during the trial were routinely on the news. The Knesset commenced an urgent discussion on the Kaplan-Herzfeld case in 2006, when the Director-General of the MOH, Prof. Avi Israeli, was constantly asked about the lack of adequate

¹⁶⁵ See Ron Resnik, Mismachai Hanisuy? Ovedet Hanikayun Betach Zrka Lapach (Trial Documents? The Cleaning Lady Probably throws them to the garbage) Haaretz (No date) available at <http://www.haaretz.co.il/hasite/pages/ShArtPE.jhtml?itemNo=759382&contrassID=2&subContrassID=2&sbSubContrassID=0> (Isr.) (last visited Sept. 7, 2012).

¹⁶⁶ In February 10 2011 the spokesman, Mr. Ron Roman, of the Justice Department issued a statement to the press explaining the decision to dismiss the case against the doctors. Roman clarified that the reason not to indict the physicians was reached due to the wide disagreement in the medical literature to several of the issues that are central basis to the alleged accusations. The spokesmen letter is available at <http://www.justice.gov.il/NR/rdonlyres/68CA90B2-EBE3-43E5-85C4-AD99E81EC387/25950/SgiratTik.doc> (Isr.) (last visited Sept. 7, 2012).

¹⁶⁷ The news regarding the MOH instigating disciplinary proceedings against 21 physicians is available at News 2 website at <http://www.mako.co.il/news-israel/health/Article-50fc6a5b5702e21004.htm> (Isr.) (last visited Sept. 7, 2012).

¹⁶⁸ Chapter 9 of the Medical Practitioners Ordinance [Amendment] Law 5736-1976 (Isr.) authorizes the Minister of Health, upon recommendation of the Director General of the MOH, to impose different sanctions including warning, reprimand and temporary or permanent license revoke.

oversight. Prof. Israeli explained that the MOH was working on fixing the problems.¹⁶⁹ At the same meeting, Prof. Reches, the Head of the Ethics Department of the Israeli Medical Association, apologized on behalf of the medical profession to the families of the participants of the Kaplan-Herzfeld case.¹⁷⁰

The MOH has responded to the public demands for stringent oversight procedures. In 2006 the Pharmaceutical Administration within the MOH revised its Guidelines for Clinical Trials in Human Subjects. These Guidelines for Clinical Trials introduced more stringent procedures for inspection, oversight and reporting mechanisms at three levels of supervision:

- a) By the Helsinki committee to supervise approved trials and to report the MOH every six months. This committee is responsible to receive annually or adverse events reports from investigators; in higher risks trials more frequent reports.¹⁷¹
- b) By the hospitals audit panel to review and monitor the ongoing clinical trials approved at the institution. The duty of the audit panel is to review actual compliance with the approved trial plan.¹⁷²
- c) By the MOH oversight by on-site inspections.¹⁷³

Lastly, the aftermath of the State Comptroller's damaging report also led to several private¹⁷⁴ and government bills initiating new legislation. Knesset Member Orlev in 2006 expressed his frustration with the current scheme: "The situation is akin to anarchy – there is no law and no judge. A man does as he pleases... Therefore, in my opinion; there is moral importance – from both the perspective of human dignity and patients' rights, and the progress of science and

¹⁶⁹ See the Knesset Labor, Welfare & Health Committee, protocol no. 80 (October 23rd 2006) available at www.aisrael.org/_Uploads/46312006-10-23-02.rtf (Isr.) (last visited Sept. 7, 2012).

¹⁷⁰ Prof. Reches expressed his need to apologize to the participants families for the horrific things done to them. He mentioned that together with the Knesset and the MOH, they will work to close the "small" gaps in the law today so things like that will never happen again. *Id.*

¹⁷¹ The Guidelines for Clinical Trials *supra* note 35 at §18.1.

¹⁷² *Id.*, at §18.2.

¹⁷³ *Id.*, at §18.3.

¹⁷⁴ Private Bills are presented by a member of the Knesset or a group of Knesset members, as oppose to government bills which are presented by a minster member of the acting government. In 2005-2006 more than three private bills for legislation was submitted to the Knesset by several Knesset Members including Polishok, Orlev and Barzinitz.

medical research –to promote legislative process so these issues will be resolved.”¹⁷⁵ [Translated from Hebrew]

To date, no additional legislation has passed. From the interviews with officials of the MOH, it seems that the MOH is currently working on revising its former bill into new legislation on the matter.¹⁷⁶ Per the MOH official, the MOH do not believe that the new bill will be approved any time soon.¹⁷⁷ The interviewee also suggested that due to the relatively high frequency of the change of government in Israel, this makes it extremely hard to advance complicated issues such as those of clinical trials in humans.¹⁷⁸

Against this background, the following section examines how the Israeli regulatory regime addressed COI within the context of clinical trials.

2.3 COI in Medical Research under the Israeli Regime

2.3.1 Statutory Provisions

COI in the context of medical research is a relatively new issue¹⁷⁹ particularly in Israel. Similar to the traditional public COI doctrine, COI in the clinical trial context derives from the ethical notion of fiduciary obligations¹⁸⁰ toward trial participants¹⁸¹ and the public at large. To control the financial ties between physicians and investigators and commercial sponsors, the Guidelines for Clinical Trials assigned several key stakeholders to oversee these financial connections. Per the Guidelines for Clinical Trials the hospital director or its designee (namely the Helsinki committee) are required to review the contractual agreement made between the sponsor and the

¹⁷⁵ See the Knesset Science & Technology Committee, protocol no. 16 (July 11, 2006) available at <http://knesset.gov.il/protocols/data/html/mada/2006-07-11.html> (Isr.) (last visited Sept. 7, 2012).

¹⁷⁶ Its former bill was originally submitted to the Knesset in 2007.

¹⁷⁷ Interview with MOH official, at the MOH offices, Israel (September, 5th 2010).

¹⁷⁸ *Id.*

¹⁷⁹ According to Krimsky in the U.S. until 1980s the COI in medical research was by in large completely off the radar. He attributed such belated attention to the issue to two prior perceptions: 1) the normative features of the system addressed the issues of COI; 2) considerable public trust interest in scientific/researchers. Krimsky, *supra* note 73 at 64.

¹⁸⁰ The relationship between researchers and participants is portrayed by the same vulnerability, trust, and protection underling the relationship between fiduciaries and beneficiaries. Arguably, such parallels make the fiduciary doctrine the adequate model for framing investigators' obligations toward subjects. See C.H. Coleman, Duties to subjects in Clinical Research, 58 Vand. L. Rev. 387 (2005).

¹⁸¹ Krimsky *supra* note 73 at 71.

research investigator.¹⁸² They are required to make sure that “...there is no conflict of interest in conducting the trial at the medical institution between the commercial company and the Investigator, employee of the medical institution.”¹⁸³

The Director-General of the MOH issued a notice, last revised in 2009, authorizing a special committee within the MOH - the “Committee for Contracts with Commercial Companies” - to review and approve trial sponsorship contract and budget plans.¹⁸⁴ This special committee is also authorized to review and approve physicians’ travel and conferences expenses as well as physicians’ continued medical education proposals. This special committee, however, is only authorized to review research budget plans or other expenses issued by government owned institutions and those owned by the Clalit Health Fund. For these institutions this is a mandatory review. Notably, although the MOH authorizing notice mandates this review process, this notice does not contain sanctions in case of breach. The special review mechanism was also offered to other research institutions in Israel, but according to a special committee official interviewed¹⁸⁵, to date excluding one hospital no other hospital has voluntarily decided to participate in it.

The regulatory review of COI begins with the “New research application form” filed by the principal investigator.¹⁸⁶ In that form, the principal and secondary investigators are required to disclose any “affiliation” to the trial sponsor. The Guidelines for Clinical Trials defines affiliation as: “A relationship of paid employment; or commercial or business relationship; or family or personal relationship; or any other relationship, including a subordinate work relationship, which could be construed as a conflict of interest or dependence; except for reimbursement of expenditures or remuneration for participation in committees...”¹⁸⁷ Hospital officials are required to review this form and based on the affiliated disclosed information, evaluate whether there is COI, and if so to eliminate it. The Guidelines for Clinical Trials, however, do not define COI, or its scope; nor do they provide clear standards for assessing what

¹⁸² See the Guidelines for Clinical Trials *supra* note 35 at §9.

¹⁸³ *Id.*, at §9.2.

¹⁸⁴ See the Director-General of the MOH Notice no. 8/04 (2004) available at http://www.health.gov.il/UnitsOffice/GeneralManager/Pages/All_files.aspx (Isr.) (last visited Sept. 7, 2012). This special committee is a joint committee appointed by the Director-General of the MOH and Clalit.

¹⁸⁵ See interview with MOH official, at the MOH official’s office, Israel (September 6th, 2010).

¹⁸⁶ This is the MOH required form, in Hebrew, used by all the hospital in Israel. The forms are available in Hebrew at the MOH website at <http://www.health.gov.il> (last visited Sept. 7, 2012).

¹⁸⁷ The Guideline for Clinical Trials *supra* note 35 at §2 of the Definitions.

type of contractual obligations constitutes a COI. The interviews conducted with hospital officials – mainly hospital directors, Helsinki committee members and the heads of R&D department – shed some light on the definitions, processes and practices currently implemented in hospitals conducting clinical trials in cases where affiliation is disclosed. Chapters 4-6 discuss in detail these interview data.

Beyond the hospitals' sponsorship-contractual evaluations, the potential COI resulting from the interaction between the industry, physicians and research institutions has come under the Israeli legislature scrutiny. In 2008 the legislature enacted a rigorous statutory disclosure and reporting provision which was later revised in 2010.¹⁸⁸ This statutory provision imposes reporting requirements of any monetary donation or donation of worth made by drug and medical device companies operating in Israel to a variety of recipients. The list of recipients is very broad and it includes nonprofit medical institutions, patients' advocacy groups, universities and physicians. This statutory provision has two central goals: 1) providing the MOH with an effective tool to manage COI in areas of health¹⁸⁹; 2) allowing more transparency in the way healthcare stakeholders are rewarded for their role in the medical products development process.¹⁹⁰ This reporting mechanism was initiated by the Ministry of Finance in the effort to oversee the cost of prescription drugs and medical device in the national healthcare budget.¹⁹¹ The 2010 revision applied the reporting mechanisms to physicians and researchers conducting clinical trials in not-for-profit institutions.

This statutory provision focuses on the appropriateness of donations paid to those who can influence either the purchase or distribution of pharmaceuticals, medical devices, and other goods and services or those who sell and distribute those goods and services. Notably, the disclosure is imposed on both the donor and the recipient.¹⁹² Disclosures are to be forwarded to

¹⁸⁸ The 2008 Amendment to §40A to the National Health Insurance Law 5723-1994 [1995] (Isr.)

¹⁸⁹ See Shelli Levy, A Report on Donation in Areas of Health: part of the New Arrangement Bill for 2011-2012, submitted to the Labor, Welfare & Health Committee in the Knesset (2010) (Isr.) available at <http://www.knesset.gov.il/mmm/data/pdf/m02689.pdf> (last visited Sept. 7, 2012).

¹⁹⁰ See Mr. Yoel Lifshitz at the Knesset Labor, Welfare & Health Committee, meeting protocol no. 444, (May 26th 2008) (Isr.) available at www.aisrael.org/Uploads/46312006-10-23-02.rtf (last visited Sept. 7, 2012).

¹⁹¹ According to the introduction section of the law, of the 30 billion NIH of the annual national healthcare spending 6 billion NIH is spent on drugs and medical devices. See the introduction to §29 of chapter 7 of the Arrangement Law 2010 available at <http://www.shituf.gov.il/discussion/285> (last visited Sept. 7, 2012).

¹⁹² With regard to physicians, the threshold for disclosure is annual donations of more than 2,500 NIH.

the MOH and will be posted onto its website. There is no doubt that by promoting such a reporting requirement, it will increase transparency allowing both the public and the MOH access to essential information relating to potential COI. Since this reporting applies to both researchers and institutions, it will enable scientists, policymakers and even the public to identify the prevalence of COI both at the individual and institutional levels.

Similar to the Israeli statutory reporting mechanism, in 2010 the U.S. enacted the Payment Sunshine Provision act.¹⁹³ Briefly, this federal law establishes a national database for any payments to physicians by medical device, medical supply, and pharmaceutical companies and, requires manufacturers of pharmaceuticals, medical devices, and biologics to publicly report money given to physicians and teaching hospitals of above the annual amount of 100 USD.

On the surface, both the Israeli and the U.S. statutory reporting provisions are very similar. However, in some respects the Israeli provision is broader than the U.S. and in other respects is it actually narrower. On the broader side, the Israeli provision requires both the donor and the recipient to report their donation, whereas the U.S. provision required only the companies giving the rewards to report. Essentially, imposing both donor and recipient to report their monetary interactions will enable better scrutiny of fraud or cross evaluations of disclosure. On the narrower side, the Israeli provision only requires the reporting of donations and not any other related fees or sale related practices, whereas the U.S. provision definition of payment is very broad. Also, to date the Israeli provision, as opposed to the U.S., does not contain any sanctions for cases of failing to report.¹⁹⁴

2.3.2 Israeli Medical Association (IMA)

Beyond legislative provisions, the Israeli Medical Association (“IMA”) has also addressed the relationships between pharmaceutical and device companies and healthcare professionals. In 2004 the IMA and the pharmaceutical organizational representatives in Israel announced their ‘Joint Ethical Convention’, in which they declared their devotion to the highest ethical standards.

¹⁹³ See Patient Protection and Affordable Care Act of 2010, 42 U.S.C. §1320q-7h (2011).

¹⁹⁴ The U.S. provisions include civil penalties provisions that cannot exceed \$150,000, unless the failure to submit information was done knowingly than the penalties will not exceed a million dollar.

This voluntary code entails commitments to allow the investigator complete freedom in the conduct of the trial and the option to publish his or her findings without any restrictions.

Along with the convention, the IMA also revised its code of ethics, and expanded their ethics training.¹⁹⁵ This code of ethics is the profession's ethical benchmark binding all physicians in Israel.¹⁹⁶ This code explicitly specifies that ties between physicians and private industry are important for medical progress and advances. At the same time, and unlike U.S. and Israeli regulations, the IMA code of ethics requires researchers and medical institutions to disclose all their financial ties with research sponsors not only to the Helsinki Committee reviewing the protocols, but also to the trial participants. The IMA code further recommends adopting primary legislation governing human subjects' research.¹⁹⁷

2.3.3 Lawyers Reaction

The lawyers' reaction was not late in coming. In 2006 Moshe Goldblat published an article at the Israeli Bar Association website regarding patients' rights for adequate information.¹⁹⁸ Goldblat discussed the various COI physicians have – both as clinicians and as researchers – and mentioned that this is common and widespread phenomenon in Israel. Goldblat is astonished that medical ethics were never codified by the legislature, despite its grave potential impact on patients' rights. His critique also relates to the lack of transparency in medical ethics teaching as the disciplinary proceedings commenced by the MOH are not published, while the cases brought to court discuss only major cases of criminal behavior. Goldblat calls for more transparency and disclosure requirements on part of physicians and the institutions the patient or participants.¹⁹⁹

On March of 2011, a class action was filed against a government hospital in the northern region and against the MOH. The class action claims that a sample from patients' liver was taken for

¹⁹⁵ The IMA is now providing on site GCP trainings to physicians/researchers on a regular basis.

¹⁹⁶ Physicians, who failed to comply with the provisions of this code of ethics, might be subject to disciplinary proceedings which may result in cancellation of membership. IMA's Code of Ethics *supra* note 123.

¹⁹⁷ *Id.*

¹⁹⁸ See Moshe Goldblat, Zechut Haholim Legiluy Naot (Patients' Right to Adequate Disclosure) (2006) available at http://www.israelbar.org.il/article_inner.asp?pgId=33126&catId=287 (Isr.) (last visited Sept. 7, 2012).

¹⁹⁹ Goldblat suggests amending the informed consent provision of the Patients Rights Law. *Id.*

medical experimentation without obtaining informed consent.²⁰⁰ The claim seeks compensation to all the patients who participated in the trial without their consent. This is the first class action filed against a medical institution and the MOH for violating their ethical obligations for informed consent in medical experimentation.

2.3.4 Judicial Scrutiny

Despite the proactive attempt to address COI by virtue of disclosure mechanisms, there is reactive judicial scrutiny through criminal prosecutions for COI and research misconduct. As the cases below illustrate, the Israeli court seems to apply a higher standard on senior physicians accused for research ethics and legal violations through the breach of trust offense. The Dicker case²⁰¹ is a good example.

Briefly, Dr. Dov Dicker was convicted in 2009 for committing among other offenses a breach of trust.²⁰² Dr. Dicker, is a well known gynecologist, university professor and the head of the hospital Helsinki committee. He submitted an article for publication to several U.S. medical journals based on fictitious clinical research.²⁰³ Suspicion brought by the U.S. editor triggered a thorough investigation of Dr. Dicker who had forged dozens of documents (including Helsinki committee approvals and participants' informed consents) to support his case. The court, in a rare step rejected the plea bargain reached with the state, and sentenced him to eight months in jail, a suspended sentence and a fine.

The court explained that since medical experts serve as a role model to others, they deserve a higher level of trust. When such trusted experts abuse the trust they are given, they deserve “condemnation” and “disgust”. The court accused Dicker for being arrogant and added that “forgiving punishment as suggested in the plea bargain can bring to the collapse of moral values or pose as a compromise on norms and values that the court is instructed to protect and

²⁰⁰ Allegedly, during adjustable gastric bands surgery conducted in anesthetization, a sample from the patients' liver was taken for medical research. As alleged, the patients were signed an informed consent form short time before the surgery began. The class action was recently submitted to the District court of Petach Tikva, See ClassA (PT)10356-03-11 *Lev Orli v. Ziv Medical Center-Zfat* (submitted March 6 2011), Nevo Legal Database (by subscription) (Isr.).

²⁰¹ See the Dicker case *supra* note 38.

²⁰² §284 of the Penal Law 5737-1977 (Isr.).

²⁰³ Dr. Dicker allegedly developed a new therapeutic treatment helping to treat women who suffer ovarian torsion (a condition that cuts the blood supply to the ovary).

endow.²⁰⁴ [Translated from Hebrew] The court also interpreted broadly the risks associated with such breach of trust. Not only does publication of fictitious research harm potential patients who were treated with an alleged proven therapeutic, but it can also undermine their trust in their doctor's practices and even in medical journals in general.²⁰⁵

In another case, Dr. Arye Figer - a well known oncologist in charge of the hospital clinical trials sponsored by drug companies - was convicted for breach of trust, abuse of vulnerable patients and bribery crimes. Dr. Figer was convicted, inter alia, for demanding money from family members of dying cancer patients in order for them to access participation in medical research on cancer therapies, and for referring patients to his private practice.²⁰⁶ Judge Berliner discussed Dr. Figer's COI and indicated that such behavior undermines the public's trust in the integrity of the health care system.²⁰⁷

Last is the Oretzki case.²⁰⁸ Dr. Gideon Oretzki – the head of the hospital cardiology surgical department – recommended the hospital purchase a medical device from a company. Dr. Oretzki failed to disclose to the Helsinki committee his financial ties with that company. Although, the Judge stated that he was convinced that Oretzki should be convicted for breach of trust due to COI, he accepted the state's argument that Oretzki did not want to gain profit but rather to help his patients. He sentenced the doctor to community service. The court indicated that a physician acting in COI for personal gain is a very severe matter, as it can open a window for corruption.²⁰⁹ Namely, physicians' moral behavior should not be driven from self-interest but rather from caring for their patients.

2.3.5 Defining COI and Risks

²⁰⁴ See the *Dicker* case *supra* note 38.

²⁰⁵ *Id.*

²⁰⁶ Per the court, in one of the accusations Dr. Figer received money from the son of a patient in order to allow the patient to receive the investigational drug instead of the standard of care. See CrimA (TA) 7512-04-10 *State of Israel v. Figer Arye* (March 2 2011), Nevo Legal Database (by subscription) (Isr.).

²⁰⁷ *Id.*

²⁰⁸ See CrimC (TA) 5848/05 *State of Israel v. Oretzki Gidion* (March 14 2006), Nevo Legal Database (by subscription) (Isr.).

²⁰⁹ *Id.*

As mentioned above, COI is defined as where professional judgment or action concerning primary interest will be overly influenced by a secondary interest.²¹⁰ In biomedical research the primary interest includes protecting participants' health, research validity and maintaining the public trust.²¹¹ Whereas the secondary interest may include financial interests resulting from the collaboration with industry or equity holding; and non-financial interests, such as pursuing professional advancements (as attributed to investigators in the Kaplan-Herzfeld case) or even ego (as discussed by the judge in Dicker case). None of these secondary interests are themselves illegitimate, as some are considered desirable professional practices.²¹² The concern is whether these secondary interests can create biases in researchers and/or in institutional decision-making practices and processes that can jeopardize the health of research subjects and research integrity.²¹³ There is a serious debate in the literature whether there is definite evidence showing that COI has indeed directly resulted in serious outcomes for patients. According to Blumenthal²¹⁴, some cases have certainly created the suspicion or the appearance that it did.²¹⁵

Emanuel and Thompson explain that COI circumstances refer to a "tendency" irrespective to actual occurrence. They explain that "tendency" to impact decision-making should be interpreted by experience, common sense and psychology research data.²¹⁶ Similarly, the Israeli courts interpret "tendency" as an objective standard determined from the lay person point of view.²¹⁷ In this way Emanuel and Thompson argue that distinction between potential and actual COI undermines the fundamental rationale in the basis of prohibiting any COI. They assert that

²¹⁰ See Dennis F. Thompson *supra* note 34 at 573-576.

²¹¹ *Id.*

²¹² These legitimate secondary interests may include scientific recognition and grant support. E.J. Emanuel & D. Thompson *supra* note 26 at 760.

²¹³ Robert Gatter *supra* note 27.

²¹⁴ See David Blumenthal, Conflict of Interest in Biomedical Research Biotech in Northeast Ohio Conference: Current Plans and Visions for the Future, *Health matrix* 12(2): 377-92 (2002).

²¹⁵ Often mentioned by the literature is the classic Jesse Gelsinger case from the 1999. Gelsinger, 18 years old, died as a result of his participation in a phase I gene therapy study at the University of Pennsylvania. Apparently, both the principal investigator and the University of Pennsylvania had financial interests in the gene therapy trial. The consent form failed to describe the type and scope of these financial interests. See Paul Gelsinger & Adil E. Shamoo, Eight Years After Jesse's Death, Are Human Research Subjects Any Safer? *The Hastings Center report*, 38(2): 25-7 (2008). Many regulation violations were revealed by FDA's investigation of the case, including providing misleading and inaccurate information in the informed consent forms and to the IRB, failing to meet participants' selection criteria etc. See Initiation of Disqualification Proceeding and Opportunity to Explain: FDA notice to Dr. James Wilson, University of Pennsylvania Institute for Human Gene Therapy (2000), available at <http://www.fda.gov/foi/nidpoe/n121.pdf> (last visited Sept. 7, 2012).

²¹⁶ E.J. Emanuel & D. Thompson *supra* note 26 at 761.

²¹⁷ See Siat Halikud case *supra* note 82.

proving actual COI encompasses the need to incorporate broad subjective rules when it is neither possible nor desirable to assess individual's actual motives. In essence when the investigator or the institution cross the line and actually alters their judgment by accepting money or other royalties, they are no longer simply in the area of COI but their violation might become a more severe offense such as abuse of power or even bribery.²¹⁸ As put nicely by Shamoo and Resnik: "...having a COI is not, in itself, research misconduct. A COI is a risk factor for misconduct."²¹⁹

Critics, particularly senior scientists, tend to view such broad interpretation of the COI rules as a personal attack arguing that such implementation is out of proportion. As one argues, prohibiting all financial ties between scientists and sponsors is: "a serious insult to the integrity of scientists working for industry. The implication of [such policy]... is that by taking their jobs they have foregone the possibility of conducting valid research."²²⁰ Another critic argues that focusing on the collaborations between industry and researchers or research institutions through wide COI rules and restrictions: "...threatens to disrupt what has been a wide-ranging and productive exchange of knowledge and information... this new regulatory philosophy are likely to degrade the quality of research and delay the provision of lifesaving medicines and treatments."²²¹

2.3.6 Different Levels of COI

Various types of conflicting interests may affect the duty to protect participants' rights or research validity. The literature describes three main areas for conflict:

Individual researcher level COI at the investigator level can arise when his or her secondary interest is either intrinsic²²² (e.g., inherent self-interest, aspirations for promotion, reputation and publication) or financially motivated (e.g., equity holding, consulting fees, or recruitment incentives). Such COI of interest is embedded in the notion that investigators have fiduciary obligations toward participants.²²³ The U.S. COI rules mostly address the concerns relating to the

²¹⁸ E.J. Emanuel & D. Thompson *supra* note 26 at 761.

²¹⁹ See Shamoo & Resnik *supra* note 14 at 192.

²²⁰ See K. Rothman, the Ethics of Research Sponsorship, *J Clin. Epidemiol.* 44 (Suppl. I) s25, s26 (1991).

²²¹ Richard A. Epstein, How Conflict-of-Interest Rules Endanger Medical Progress and Cures, Manhattan Institute for Policy Research (2010) available at http://www.manhattan-institute.org/html/fda_03.htm (last visited Sept. 7, 2012).

²²² See Du Val *supra* note 11.

²²³ See Krinsky *supra* note 73 at 67.

effects of researcher's financial COI and not other intrinsic interests. Per Thompson, the reason the focus is on financial gain is not because such interest is more harmful than other secondary interests, but rather because "it is more objective and more fungible. Money is easier to regulate by impartial rules."²²⁴ Additionally, Emanuel and Thompson argue that there is relatively small debate in the literature on whether financial interest should be prohibited as secondary interest as oppose to intrinsic interests where some argue that professional recognition might be regarded as primary interest.²²⁵ Thompson further rejects the critics who argue that since there is no good way to evaluate non-financial COI, why should we bother about financial COI? Thompson argues that simply because intrinsic interests are hard to assess does not mean that we should disregard financial interests.²²⁶

In Israel the judicial and scholarly material suggests a broader interpretation and implementation of the COI doctrine. As discussed above the courts are willing to enforce criminal proceedings when it is objectively perceived that the public's trust was undermined regardless of the nature of the conflicted interest. Support for such a broad approach can be found in Dicker's case (attempt to publish fictitious research), where the judge explicitly stated that the fact that Dr. Dicker had no financial gain is irrelevant. Dr. Dicker's "ego" was regarded as the conflicted interest enough to result in criminal conviction. The court also broadly interpreted the potential risks involved in such conduct. Not only was the court concerned about the health of potential patients being treated with such fictitious treatment, but also concerned about how this would affect the trust these potential patients have for their treating physicians.

Despite the courts' wide application of COI doctrine, the regulatory scheme is somewhat limited. Individual researcher COI was explicitly addressed in the Israeli Guidelines for Clinical Trials. As discussed above, the regulatory regime requires disclosure on part of the investigators of any affiliation to the trial sponsor. The regulations is silent to other possible COI such as when the investigator is indeed the sponsor or rather when they own the patent rights to the research subject matter. The regulatory scheme is also silent to COI circumstances by virtue of financial

²²⁴ Thompson *supra* note 34 at 291.

²²⁵ E.J. Emanuel & D. Thompson *supra* note 26 at 760.

²²⁶ Thompson *supra* note 34 at 291.

ties with a rival sponsor company that seeks negative outcome of the trial.²²⁷ Chapter 4 will discuss in depth how the Israeli regime identifies, assesses and manages such COI in the absence of regulatory guidance.

*Research Reviewer level*²²⁸ Institutional ethics committees (Helsinki committee in Israel) or government advisors are charged primarily with reviewing research protocols to analyze potential ethics violations and with acting as “gatekeepers”²²⁹ for the evaluation and oversight of human subject research. Similar to individual researchers, COI can arise in relation to these research reviewers themselves. A classic example of potential COI of a committee member is when he or she holds equity interest in a company that sponsors studies reviewed by him or her.

As opposed to rich and reliable empirical research on researcher’s COI in the U.S., very little data exist on the extent of the impact COI has on the members of Israel’s institutional ethics committees or government advisory committees. The U.S. FDA’s federal regulations mandate recusal of the ethics member from participating in IRB (Institutional Review Board) review if they have a COI.²³⁰ In Israel the biomedical regulatory regime does not formally address such COI. However, general statutory provisions, and the State Comptroller specific guidelines may apply. Notably, unlike the U.S., Israel does not have private IRBs with fee-based contractual relations with sponsors. The Helsinki committee in Israel is hospital based and only reviews research applications submitted by research employees of the institution.

Chapter 5 will discuss in detail the issues relating to institutional committee members and government advisors’ COI particularly the interview data shedding some light on current procedures and practices. Chapter 5 will also devote significant attention to the COI of the various experts and advisory committees (mainly the National Committee) that provide the MOH with their scientific and ethical input.

²²⁷ E.J. Emanuel & D. Thompson *supra* note 26 at 762.

²²⁸ Jeffrey Groeger & Mark Branec, Conflict of Interest in Human Subjects Research, *Critical Care Medicine* 31 (3 Suppl): S137-42 (2003).

²²⁹ Gerald Schatz, Are the Rationale and Regulatory System for Protecting Human Subjects of Biomedical and Behavioral Research Obsolete and Unworkable, or Ethically Important and Inconvenient and Inadequately Enforced?, 20 *J. Contemp. Health L. & Pol’y* 1 (2003-2004).

²³⁰ 21 CFR 56.107(e).

Institutional level COI may occur when institutions or their senior decision-makers have financial interests that might impact the institution's professional judgment regarding the protection or oversight of research.²³¹ In the U.S. public non-for-profit institutions' discoveries are often patented by these institutions and then licensed to the industry for commercialization.²³² Public non-for-profit institutions may also hold equity or own start-up companies to develop their employees' discoveries; or receive financial rewards for administering a trial or accept recruitment incentives. The concept of institutional COI is relatively new and little empirical data has been collected in this regard. In the U.S., the Office of Inspector General (OIG) report of 2011 studied institutional COI at several NIH grantee research institutions. The OIG found that eighteen of the twenty-one institutions identified at least thirty eight institutional conflicts related to NIH research grants in fiscal year 2008. The OIG also found that institutions with written institutional COI policies and procedures were more likely to identify conflicts than those who did not.²³³

Unlike researcher COI, to date in the U.S. and Israel there are no statutory provisions that directly govern the institution's COI. In the U.S., several regulatory agencies and professional associations have promulgated guidance on the issue, such as the OIG report, or the joint report issued by the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU).²³⁴ The AAMC-AAU report, for example, urged its member institutions to develop and apply comprehensive institutional COI policies. They also recommend that the research and financial related decisions should be separated. However, despite the numerous guidelines and the attention given to the issue both by professional organizations and federal agencies, it seems that in practice most U.S. medical schools have given little attention to it.²³⁵

²³¹ L. Hampson, J. Bekelman & C. Gross, *Empirical Data on Conflict of Interest in the Oxford Textbook of Clinical Research Ethics*, 676 (Emanuel E. at el. ed. Oxford 2008).

²³² See MM. Johns, M. Barnes, PS. Florencio, *Restoring Balance to Industry-Academia Relationships in an Era of Institutional Financial Conflicts of Interest Promoting Research While Maintaining Trust*, JAMA 289(6), 741-746 (2003).

²³³ See Off. of Inspector Gen., Dep't of Health and Human Serv., OEI-03-09-00480, *Institutional Conflicts of Interest at NIH Grantees* (2011), available at <http://oig.hhs.gov/oei/reports/oei-03-09-00480.pdf> (last visited Sept. 7, 2012).

²³⁴ Ass'n of Am. Med. Colls., *Protecting Patients, Preserving Integrity, Advancing Health: Accelerating the Implementation of COI Policies in Human Subjects Research* (FEB. 28, 2008) (hereinafter: AAMC-AAU Report).

²³⁵ Per Shamoo & Resnik, a study conducted in 2008 shows that only 38 percent of all U.S. medical schools have institutional COI policies. They thus assert that per this survey most medical schools show little interest in dealing with institutional COI. See Shamoo & Resnik *supra* note 14 at 195-198.

Chapter 6 will discuss in depth the current forces and trends in the Israeli public and government hospitals toward a for-profit management model and how they could allegedly generate financial COI at all levels of the institutional structure. Furthermore, as discussed in Chapter 6, the Public Health Regulations themselves might be intensifying these institutional COI since they require that each institution's ethics committee include a representative affiliated with the institution's management.²³⁶ They ensure that the institution's interests are a significant part of the ethical evaluation and decision-making processes. This concerns how well the risks associated with COI are advocated and protected in research and by whom. Another issue discussed in Chapter 6 is the newly mentioned government plan allowing publically funded institutors to retain patent rights, and how that will affect COI at the hospitals.

2.4 Conclusion

The global entrepreneurialism of public biomedical research and close ties with private sector has introduced powerful financial incentives in to the public arena. In Israel, through powerful forces of privatization, influenced by the U.S. model, the competitive research enterprise was enhanced. The Israeli current regulatory scheme – mostly self-regulated organizational policy - and economic priorities, have been gradually allowing entrepreneurial incentives of medical research in public institutions and scientists to flourish. At the same time, scandals, constant media coverage, and rigorous judicial scrutiny, have raised concerns questioning stakeholders in charge of conducting, overseeing and evaluating research commitment to scientific and ethical standards due to COI. In light of public outcry, the government has initiated mechanisms aimed to limit the potential negative influence of these commercial COI in virtue of disclosure (imposed on scientists or government advisors) and reporting mechanisms (imposed on scientists, institutions and the private sector). These mechanisms potentially portray the moral and political characteristic of the regulatory environment in Israel, aiming to enhance elements of accountability and transparency within the realm of medical research.

The question raised is whether the government created mechanisms are adequate responses to the influence of commercial incentives and values on the mostly self-regulated research landscape.

²³⁶ See Public Health Regulations *supra* note 138 at §1, second Appendix.

This concerns how well the risks associated with COI are advocated and protected in research under the current scheme and by whom. In order to answer these questions, the next chapter provides a comprehensive study of the structure, standards and processes currently in Israel's clinical research infrastructure.

CHAPTER 3: Israel Biomedical Jurisprudence, Infrastructure and Processes

“Why is all this happening in Israel? I’ve never seen so much chaos and so much innovation all in one tiny place.”

[Jessica Schell, Vice President NBC Universal Inc]²³⁷

This thesis examines the governance, operations and practices by Israel’s biomedical regulatory scheme to safeguard against the risks associated with COI in biomedical research. To understand how the current regulatory framework safeguards the risks associated with COI in Israel, this chapter provides an overview of the structure, standards and processes of Israel’s clinical research infrastructure. This chapter is designed to demonstrate the internal conflict between on the one hand the government’s political and economic agendas promoting the competitive enterprise of scientific research and on the other, the efforts to protect research participants from the potential risks such enterprise may pose on their safety and wellbeing. To better understand Israel’s commercial biotechnology environment and its crucial influence on clinical research processes and practices, in six sections this chapter describes several key factors. Following a brief introduction to Israeli biomedical arena, section 3.2 analyzes the context in which the biomedical sector operates, namely Israel’s biomedical normative jurisprudence. Then section 3.3 focuses on Israel’s political commitment and instrumental initiatives that promote innovation and commercialization, as well as the government’s strategies and policymaking approach.

Section 3.4 describes the stakeholders involved in clinical research, their collaborations and influences, and section 3.5 focuses on Israel’s clinical research infrastructure and its impact on the various stakeholders’ interactions. The comprehensive study of the regulatory infrastructure highlights the central role the medical institutions, particularly the Helsinki Committees, and the MOH play in safeguarding both the rights of human participants and the scientific validity of the research. Explicitly, the regulatory mechanism imposes upon the hospitals and the MOH the

²³⁷ A quote taken from a 2008 interview conducted by authors Senor & Singer with the vice president of NBC Universal Inc., Jessica Schell, as mentioned in the book by Dan Senor & Saul Singer, *Start-up Nation: The Story of Israel's Economic Miracle*, 16 (2009).

responsibility to identify and manage COI situations arising from the financial or contractual relationships between trial sponsors and investigators. The discussion of the regulatory framework in this chapter, serves as a theoretical benchmark for the analysis in chapters 4-6 regarding the practical interpretation and implementation of the regulatory infrastructure. Section 3.6 summarizes and concludes the discussion.

3.1 Introduction

Within the last decade, Israel has become a worldwide leader in biotechnology research and a leading investor in bio-therapeutics designed to treat neurological disorders, cancer and autoimmune syndromes. In 2009, Israel ranked *first* worldwide in the total number of U.S. patents granted per capita for medical devices and *second* in the biopharma area²³⁸. Israel conducts nearly seventy percent of all clinical trials in the Middle East²³⁹. It ranks *fifth* in the number of scientific articles submitted per capita, and more Israeli companies are listed on the NASDAQ exchange than all European companies combined.²⁴⁰ Teva Pharmaceutical Industries Ltd., headquartered in Israel, is the largest generic drug manufacturer in the world.

Moreover, multinational pharmaceutical and medical device corporations as well as contract research organizations (CROs) are continuously investing in R&D units in Israel. Many of these companies also have subsidiaries and/or divisions in Israel, including Pfizer Inc., Merck and Co., Inc., and Novartis AG. The impact of multinational company investments on Israel's GDP has been substantial.²⁴¹

To better understand Israel's commercial biotechnology environment, the next section discusses Israeli jurisprudence and its endeavors to protect human trial participants as well as general medical patients.

²³⁸ Israel Life Science Industry website profile report, The Israeli Life Science Industry: 2001-2010 report: A Decade of Growth, available at http://www.ilsa.org.il/industry_profile.asp (last visited Sept. 7, 2012).

²³⁹ This is per the information available at the U.S. National Institute of Health registry's database, available at <http://clinicaltrials.gov/ct2/search/map/click?map.x=456&map.y=181> (last visited Sept. 7, 2012).

²⁴⁰ See Start up Nation *supra* note 237 at 11.

²⁴¹ Ahuva Koren *supra* note 49.

3.2 Israel Biomedical Normative Jurisprudence – Broad Protection for Patient and Participants’ Rights

In order to fully understand the purpose of protecting against COI associated risks to research participants in clinical trials, it is important to first explore Israel’s stand on the protection of trial participants in general. By and large, Israeli society regards health as a dominant value and medical science as showing great potential to heal and alleviate suffering.²⁴² Given this mindset, Israelis have eagerly taken part in clinical trials.²⁴³ In light of the importance of ethics for the conduct of medical research along with the relatively high rates of trial enrollment, it is not surprising that Israel has promulgated laws, regulations, and guidelines governing research ethics to protect the rights of patients, trial participants, and scientific validity.

Israeli jurisprudence acknowledges and provides constitutional protection for individual civil rights. Consequently, the legislature recognizes the right to protect any person’s life, body and dignity.²⁴⁴ In fact, this protection was deemed sufficiently important to have been elevated to a Constitutional right in 1992.²⁴⁵ Israel’s general normative biomedical jurisprudence acknowledges and provides a high level of protection to both medical patients and research participants, based on a liberal approach to human rights. The notion of providing this high level of protection to patients and trial participants is consistent with the essential values of personal liberty and privacy.

Israel’s Patient’s Rights Law enacted in 1996 “...aims to establish the rights of every person who requests medical care or who is in receipt of medical care, and to protect his or her dignity and privacy.”²⁴⁶ Consequently, the law acknowledges a person’s right to medical care²⁴⁷ that is

²⁴² C. Shalev, Reclaiming the patient's voice and spirit in dying: an insight from Israel, *Bioethics* 24(3) 134-144 (2010). Shalev argues that the Israeli public is generally trustful of scientific progress.

²⁴³ See Ahuva Koren *supra* note 49.

²⁴⁴ These rights were formulated in the Basic Law: Human Dignity and Liberty, 1992, [Constitution] (Isr.) at §4.

²⁴⁵ §2 of the Basic Law: Human Dignity and Liberty establishes that: “The life, body or dignity of any person shall not be violated.” With the enactment of several certain Basic Laws in Israel, the legislature granted a normative superiority stance to the rights incorporated in these laws, elevating them to Constitutional rights. A brief history of the “Constitutional revolution” in Israel can be found in Dr. Yehiel S. Kaplan, *The Right of a Minor in Israel to Participate in the Decision-Making Process Concerning His or Her Medical Treatment*, 25 *Fordham Int’l L.J.* 1085 (2002).

²⁴⁶ See Patients' Rights Law, 5756-1996, SH No. 729 §1 (Isr.).

²⁴⁷ *Id.* at §3. It should be noted that this Law represents an important shift in the Israeli health care model from a paternalistic one to a patient-based model.

appropriate and continuous,²⁴⁸ prohibits discrimination in medical treatment,²⁴⁹ recognizes the right to access medical information,²⁵⁰ and respects patients' autonomous choices.²⁵¹ In fact, in the 1999 *Daaka* case²⁵², the Israeli Supreme Court acknowledged the patient's autonomous right as an independent cause of action warranting remedy in itself under tort law.

In 2000 the Israeli legislature enacted the Genetic Information Law. This law specifically regulates the conduct of genetic testing²⁵³ in Israel, protecting the identity and privacy of the individual. The law stipulates that genetic testing can be done only in accredited laboratories and genetic testing for research purposes must also be approved.²⁵⁴ Specifically this law covers issues such as genetic counseling, prohibition of employment and insurance discrimination based on genetic information, and limitations on genetic testing of children and the incapacitated.²⁵⁵

Finally, the National Health Insurance Law stipulates mandatory unified basic health coverage for all Israeli residents by one of four regulated competing health funds (similar to U.S. Health Maintenance Organizations) discussed below.²⁵⁶ This law requires the health plans to offer a basic health benefits package to all Israeli residents without discrimination based on any grounds.

Specifically for the conduct of clinical trials involving human participants, Israel has two governing regulations: (1) the Public Health Regulations governing clinical studies in human

²⁴⁸ *Id.*, at §§5 and 8, respectively.

²⁴⁹ The Law prohibits discrimination on the grounds of religion, race, sex, nationality, and country of birth or other similar grounds. *Id.*, at §4.

²⁵⁰ *Id.*, at §18.

²⁵¹ *Id.*, at §13.

²⁵² CA 2781/93 *Ali Daaka v. Carmel Hosp., Haifa* [1999] Isr.SC 53(4) 526. In this case, the claimant's consent to undergo surgery on her shoulder was obtained just before she supposed to undergo another surgery on her leg. She was under the influence of anesthetizing drugs, and apparently no explanation of the potential risks was provided to her. The claimant suffered damages to her shoulder.

²⁵³ The Genetic Information Law, 5761-2000 (2000) (Isr.) §2, defines "Genetic Testing" as "...the testing of the DNA sample of a person in order to characterize and compare DNA sequences."

²⁵⁴ *Id.*, at §3.

²⁵⁵ *Id.*, at §§ 29 and 30 prohibit employers and insurance companies from requiring an employee/insured provide or undergo genetic testing and prohibits them to discriminate based on such genetic data. Violating such provisions may result in one year in prison or large fines based on the Penal Code, §38.

²⁵⁶ The National Health Insurance Law, 1994, S.H. 156 (Isr.) As discussed below, these health funds are independent non-profit organizations, but at the same time they are heavily regulated by the government and receive funding from it.

subjects)²⁵⁷, and (2) the Guidelines for Clinical Trials in Human Subjects 2006 governing clinical trials.²⁵⁸ In addition to the mentioned Public Health Regulations and Guidelines for Clinical Trials, Israel has other applicable rules and guidelines, which include: pre-state British mandate ordinance regulations²⁵⁹; international documents, such as the Nuremberg Code²⁶⁰ and the Declaration of Helsinki²⁶¹; the MOH procedures notices; and the Good Clinical Practice (GCP) Guidelines issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).²⁶²

Public Health Regulations require that all research involving human subjects be conducted in accordance with its and the provisions of the Declaration of Helsinki. The Guidelines for Clinical Trials explicitly acknowledge two crucial values: the safeguarding of human participants and scientific integrity.²⁶³ The Declaration of Helsinki, explicitly adopted by the Public Health Regulations and Guidelines for Clinical Trials, recognizes the need to protect the “...life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.”²⁶⁴

Both the Public Health Regulations and the Guidelines for Clinical Trials have acknowledged and implemented these rights through various requirements. These requirements include very

²⁵⁷ The Director General of the MOH was authorized to regulate hospitals and medical clinics operations according to §33 of the Health Ordinance, 1940, P.G. 1065 (adopted by the Israeli state). According to Prof. Glick, enacting the biomedical review and approval processes in Israel a few years' after the U.S. did was mainly because the Israeli society is characterized by a strong paternalistic approach particularly in medical care, and health professionals were viewed as healers concerned about the safety of their patients thus, protecting patients/participants' rights was not viewed as needed. See Simon Glick, Medical Experimentation on Humans, *Asia: articles, summaries and reports of Halacha and Medicine* 16 (3-4): 66-73, 1998 (Isr.), available at <http://www.daat.ac.il/daat/kitveyet/assia/nisuyim-2.htm> (last visited Sept. 7, 2012).

²⁵⁸ Guidelines for Clinical Trials *supra* note 35.

²⁵⁹ The Health Ordinance, 1940, P.G. 1065, was a British Mandate ordinance adopted upon the formulation of the State of Israel in 1948. This ordinance provides the legal ground for the Public Health Regulations, authorizing the Director General of the MOH to regulate hospitals and medical clinic operations. See *Id.* §33.

²⁶⁰ The Code was included in the 8/19/1947 verdict as dicta as part of the Nuremberg Military Tribunal's decision in the case of United States v. Brandt. See the Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Nuremberg, October 1946–April 1949.

²⁶¹ Israel's 1980 Public Health Regulations adopted the 1975 version of the Declaration. For a copy of the current Declaration of Helsinki see *supra* note 33.

²⁶² The ICH GCP *supra* note 52.

²⁶³ Per the Guidelines for Clinical Trials, compliance with these provisions “...is designed to protect the trial participants and ensure that their rights, safety and wellbeing are maintained, and that the information obtained from the study is reliable.” See the General section of the Guidelines for Clinical Trials *supra* note 35.

²⁶⁴ See the Declaration of Helsinki *supra* note 33 at §11.

detailed provisions for the informed consent process,²⁶⁵ risk-benefit analyses for the trial and trial participants,²⁶⁶ and clearly defined eligibility criteria for participant selection detailed in the research protocol.²⁶⁷ Moreover, the Guidelines for Clinical Trials state that the trial sponsor must continue to provide the investigational product to trial subjects for up to three years after trial, should that product prove to be beneficial.²⁶⁸ This ethical requirement acknowledges the sponsor's obligation to be responsive to the health needs of trial participants even after the study's completion.²⁶⁹

Lastly, the Guidelines for Clinical Trials require that sponsors seek adequate insurance against risks to cover compensation to injured trial participants.²⁷⁰ By way of comparison, in the U.S. according to a 2008 *New England Journal of Medicine* study, only 16 percent of academic research institutions in the U.S. provide free care to injured subjects. There is currently no available information regarding trials at other venues such as CROs and private company trials.²⁷¹

The role of identifying, reviewing and evaluating these regulatory requirements was put into the hands of the medical institution's ethics review boards and the MOH. According to the Public Health Regulations, all clinical studies on human subjects conducted in medical institutions in Israel must be approved by: (1) the medical institution's governing Helsinki Committee (Israel's medical institution ethics board) with the approval of the institution's director, and/or (2) the

²⁶⁵ See §3 of the Guidelines for Clinical Trials *supra* note 35.

²⁶⁶ According to *Id.*, at §1.3 (a), the Ethics Committee will not approve a trial on human unless: "...the expected benefits to the trial participant and to society justify the risk and the discomfort to the trial participant." As well as §1.3(e) "The foreseeable risks to the trial participant are minimized to the greatest extent possible by the use of appropriate research methods, and, where possible, the use of procedures already performed on human subjects or tested in animals."

²⁶⁷ See *Id.*, at §1.3(f).

²⁶⁸ According to §17 of the Guidelines for Clinical Trials, the decision is subject to the principal investigator's (PI) evaluation that no alternatives exists. It should be noted that both the PI and the sponsor have the right to appeal this decision. *Id.*

²⁶⁹ This requirement is limited to the circumstances where the investigational product will be reasonably unavailable to the trial participant, see *Id.*, at §17.1. Assuming that the product/knowledge obtained from the research could not become reasonably available for the benefit of the research subjects, the research might be considered exploitative and, thus, unethical.

²⁷⁰ *Id.*, at §1.3(j).

²⁷¹ See Carl Elliott & Roberto Abadie, Exploiting a Research Underclass in Phase 1 Clinical Trials, 358 *New Eng. J. Med.* 2316 (2008).

Director General of the MOH or its designees.²⁷² These institutional review committees and the MOH play a significant role in evaluating any potential or apparent ethics breaches throughout the duration of the trial, acting as “gatekeepers” to safeguard the rights of human subjects involved in the study.²⁷³

In summary, Israeli jurisprudence is designed safeguard the wellbeing and dignity of patients and trial participants. The regulatory scheme intends to protect the rights of trial participants throughout the trial, starting with the informed consent processes, and proceeding to the sponsor’s commitment to supply tested drugs for three years after trial completion. Nevertheless, as discussed in later chapters, the current scheme and safeguards thereof are lacking standards, norms and processes to address the risks to research participants associated with COI circumstances.

3.3 Israel Political and Economic Initiatives that Promote Innovation and Commercialization

Israel’s robust growth and innovation in the biomedical sector has immense importance to the country’s economy and therefore holds significant political weight. The Israeli government’s expenditure on research and development as a percentage of its GDP is higher than any member country in the Organization for Economic Co-Operation and Development (OECD),²⁷⁴ including the U.S., Germany and Japan.²⁷⁵

In 2000 the Office of the Chief Scientist in the Israeli Ministry of Industry and Trade initiated a 10 year plan, called “Bioplan 2000-2010.”²⁷⁶ According to the Bioplan, the government allocated 100 million USD for biotech pre-seed entrepreneurial funding, supporting R&D companies to enable clinical drug development and promoting domestic and private investments for more efficient technology transfer between academia and industry. The government acknowledged

²⁷² See §§2-4 of the Public Health Regulations *supra* note 138.

²⁷³ See Schatz *supra* note 229.

²⁷⁴ For more information about the Organization for Economic Co-Operation & Development (OECD) and its member countries, see their website at www.oecd.org (last visited Sept. 7, 2012).

²⁷⁵ See the Israeli Ministry of Industry, Trade and Labor’s Foreign Trade Administration Investment Promotion Center report (2006), available at www.investinisrael.gov.il (last visited Sept. 7, 2012).

²⁷⁶ For more information about the Office of the Chief Scientist support for biotechnology commercialization please see its website at <http://www.moital.gov.il/>.

that enhancing the commercialization of Israeli biotechnology products has become a national priority.²⁷⁷

In 2005, Israeli exports in life science products -- including biotechnology and pharmaceutical sales -- reached \$3.4 billion, representing 13.1 percent of all Israeli industrial exports.²⁷⁸ This national agenda of defining biotechnology as a preferred sector also attracted many citizens to study and work in the industry. As a result, Israel has the largest population of scientists per capita in the world, with 35 percent of its research focused on life science disciplines.²⁷⁹ Further, the Israeli government provides generous and unique incentives packages for companies interested in developing R&D or manufacturing facilities in Israel, including specific grant programs and tax benefits.²⁸⁰

In sum, the Israeli government's national commitment to promoting innovation and commercialization, and its significant monetary incentives, has enabled biotechnology research and development to thrive.

3.4 Israel Biomedical Research Stakeholders

3.4.1 The Key Stakeholders Providing Healthcare Services

To understand the relevant actors and their role in the biomedical research arena, a brief description of the health care system in Israel is vital. The distinctive structure of the Israeli health care system was shaped largely from the notion that society as a whole should be responsible for the health of its citizens.²⁸¹ This crucial concept has been reflected in the design of health care services in Israel, bringing together government actions, non-profit health plans and nonprofit organizations. Israel's health system infrastructure was originally developed by: the British Mandate scheme (operated in the region prior to Israel's establishment in 1948), the Israeli government, the MOH, voluntary sickness funds (or health plans)²⁸², and the Hadassah

²⁷⁷ *Id.*

²⁷⁸ *Id.*

²⁷⁹ *Id.*

²⁸⁰ See the Ministry of Industry, Trade and Labor report *supra* note 275.

²⁸¹ See Rosen Et Al. *supra* note 57.

²⁸² These sick funds were originally established by workers' associations in the beginning of 20th century to provide medical care to their members as well as to employ immigrant doctors. To find out more about the development of the Israeli health system in its early stage, see *Id.*

Medical Organization. These key players structured and implemented health care services at the beginning of the 20th century and still play a crucial role in Israeli health care and clinical research today.

Health Plans The original sick fund organizations evolved into four non-profit health plans that currently operate in Israel: Clalit Health Services (Clalit), Maccabi Healthcare Services, Meuhedet Health Services and the Leumit Health Fund. Two of these four plans were until fairly recently closely linked to Israel's political parties.²⁸³ The most prominent of the four is Clalit, which own more than thirty percent²⁸⁴ of the general hospital beds in Israel under the state regulations and has an extensive national network of health care clinics that directly employ physicians and other health professionals.²⁸⁵

Government The Israeli government is a unitary state (as opposed to a federal one) operating through administrative divisions at the regional level. The government plays a central role in the health care system. It currently owns twenty four percent of all medical institutions operating in Israel, the vast majority of which provide psychiatric services. The government-owned hospitals accounts for almost thirty percent of the overall hospital beds in the country²⁸⁶ and directly employ their own physicians.²⁸⁷ Additionally, the government acts as health provider for other services not provided by health plans, such as inpatient and outpatient psychiatric health services as well as preventive services such as immunizations and maternity care.

The government is responsible for the overseeing, licensing and overall planning of health care. Namely, it is in charge of the annual budget, deciding how funds will be allocated to health care

²⁸³ The Kupat Cholim Clalit owned by the Histadrut (Israel's General Federation of Labor) had been closely tied to the Labor Party. The triangle relationship between the three enable them to become a "sub-government" as the Clalit provide services to its members and revenues for its parent organization, which supplies political support to the Labor Party. The Leumit health plan was tied to the revisionist political parties. See D. Chinitz *supra* note 152.

²⁸⁴ See the Ministry of Health report, information on Hospitalization Institutions in Israel (2008) (Isr.), available at http://www.old.health.gov.il/download/docs/units/comp/ma2008/part1/clali_2.pdf (last visited Sept. 7, 2012).

²⁸⁵ See Health Care Systems in Transition *supra* note 57.

²⁸⁶ See the MOH report, Hospital Beds & Licensed Work-Stations (2010) (Isr.), available at http://www.old.health.gov.il/Download/pages/Beds_jan_2010.pdf (last visited Sept. 7, 2012).

²⁸⁷ For information regarding the latest statistics on hospital beds by ownership as of 2010, please see the Ministry of Health report (2010) (Isr.), available at

<http://www.old.health.gov.il/pages/default.asp?maincat=2&catid=514&pageid=5295> (last visited Sept. 7, 2012).

services.²⁸⁸ As discussed in details in Chapter 6, in the mid 1980s, to lower the budgetary deficit, the government began the process of privatizing hospitals.²⁸⁹ It also began to deregulate public medical institutions.²⁹⁰ Thus, some government-owned hospitals began implementing business-like organizational schemes to maximize profits.²⁹¹ Independent trust funds were established within these hospitals. With these processes in place, the government's expenditure on health has gradually declined and, as of 2007, amounts to 7.7 percent of the GDP.²⁹² Attempts to further reduce the government's role as a health care provider, however, have failed.²⁹³

Moreover, the government subsidizes the vast majority of health plan operations in Israel under the National Insurance Law.²⁹⁴ With such control over the health plans' budgets, it basically controls their activities, predominantly in regard to their budgeting and the services package they offer to their members. The government also dominates the pharmaceutical sector; it approves their sales, determines what drugs should be offered by the health plans to their members, sets maximum prices, licenses pharmacists, and regulates the pharmaceutical market.

Hadassah The Hadassah Medical Organization, part of an American based organization,²⁹⁵ is another important stakeholder. Hadassah is a nonprofit organization which owns two medical centers in Jerusalem that provides health care services to nearly a million people in the Jerusalem metropolitan area.²⁹⁶

²⁸⁸ In fact, the Government's decision on how much it will allocate to health care is highly politicized. See Health Care Systems in Transition *supra* note 57.

²⁸⁹ See Dani Filc *supra* note 144.

²⁹⁰ See Filc *supra* note 145.

²⁹¹ *Id.*

²⁹² Private out-of-pocket payments have been increased to cover reductions in the Government's direct spending on health services. See Chinitz *supra* note 152.

²⁹³ These attempts were essentially rejected by the physician workers union concerned that such a move would reduce their job security and pensions. See *Id.*

²⁹⁴ The money is collected by the National Insurance Institute through a health tax, in accordance with the National Insurance Law.

²⁹⁵ The Hadassah Medical Organization, currently owned by the Women's Zionist Organization of America Inc. (a volunteer women's organization in America), was originally founded as a women's organization in 1912 by Henrietta Szold, an American Jew, to provide medical aid for women in Jerusalem. The organization first established baby clinics and infirmaries in Israel and later established hospitals and other medical institutions and schools throughout Israel. Over time, with the development of the health system in Israel, the Hadassah organization has turned over most of its clinics and institutions to the government. Nevertheless, Hadassah still maintains two medical centers in Jerusalem: Hadassah Medical Organization in Ein Kerem and in Mount Scopus.

²⁹⁶ For more information about Hadassah Medical Organization operations, see their website, available at http://www.hadassah-med.com/English/Eng_MainNavBar/About/Facts+and+Figures/ (last visited Sept. 7, 2012).

3.4.2 *The Key Stakeholders Involved in Clinical Research*

The relatively young and robust growth of the Israeli clinical research industry has introduced many other relevant stakeholders and placed a spotlight on the existing functions of the MOH. These relevant stakeholders range from researchers, sponsors and CROs to academic institutions, hospitals and the MOH. To understand the current Israeli biomedical research infrastructure and operations, it is imperative to briefly discuss these primary actors' role and responsibilities.

The Ministry of Health (MOH) The MOH is a government regulatory and supervisory agency in charge of safeguarding and promoting the health of the Israeli population. The Minister of Health²⁹⁷ serves as the political head of the MOH, and appoints a physician to serve as the MOH Director-General. Among the many MOH operative and regulatory functions are: planning and establishing public health goals and controlling communicable diseases, supervising budgets and costs, providing medical services and operating a large share of the state's hospital beds, regulating and monitoring nongovernmental medical institutions (including hospitals and labs),²⁹⁸ and regulating health care professionals.²⁹⁹

As part of its policymaking function, the MOH drafts various health care related laws for the approval of the Knesset (the Israeli Parliament) and subsequently enacts regulations to these laws. Notably, the biomedical Public Health Regulations and Guidelines for Clinical Trials, discussed above, were enacted by the Director General of the MOH and the Pharmaceutical Administration Department within the MOH (respectively).

As part of the MOH's role in supervising the health of the population, it reviews and approves certain clinical trial applications, as described below, and supervises at random on-site inspections to evaluate the regulatory compliance of medical institutions.³⁰⁰ Relevant to the discussion of COI in medical research, the MOH is responsible for evaluating and monitoring

²⁹⁷ Binyamin Netanyahu, the current Israeli Prime Minister, serves as the Minister of Health.

²⁹⁸ For more discussion about the MOH's key responsibilities, please see *Health Care Systems in Transition supra* note 57.

²⁹⁹ Part of this role, planning and supervising the physician's specialization system and continuing education in medicine, was delegated to the Scientific Council of the Israeli Medical Association. For more information on the Scientific Council of the IMA, please see their website at <http://www.ima.org.il/en/CategoryIn.asp?id=161&tbl=tblCategoryabout&level=4> (last visited Sept. 7, 2012).

³⁰⁰ See *Guidelines for Clinical Trials supra* note 35 at §18.

conflicting interests at two levels of review: at the level of the individual researcher and at the level of government advisor.

With regard to potential COI at the investigator level, officials at the MOH review and approve contractual agreements made between commercial companies and government-owned institutions for research and other services.³⁰¹ This function requires MOH review of all research applications submitted in state owned hospitals and hospitals owned by Clalit³⁰². This review is conducted by the MOH's 'Committee for Contracts with Commercial Companies' ("MOH Special Committee"). As discussed in detail in Chapter 4, this MOH special committee evaluates the relation between the proposed budget plan for the trial and the commitments and responsibilities of that trial. This committee also reviews and approves payments made by the industry for any travel expenses for conferences, continued medical education and other professional activities. The MOH can delegate the review and approval function to the director of the medical institution. Upon its delegation, this hospital director must report to the MOH's special committee who has the option to overrule any contractual approval made by director.³⁰³

The MOH issues specific guidelines for COI and protection of privacy of information applicable to any member of the various government advisory committees who provide their professional opinion to the MOH ("COI Guidelines").³⁰⁴ These COI Guidelines provide detailed disclosure requirements along with a process for identifying and/or managing COI by MOH advisors. The guidelines further impose the task of review and enforcement upon the committee coordinator as well as the MOH's legal department. The goal of these COI Guidelines is to neutralize of the

³⁰¹ The authority of the MOH to review commercial contracts made between commercial companies and government-owned hospitals is fairly recent. The Procedures for reviewing contractual agreements with MOH's owned medical institutions and the Clalit Health Services was issued in April of 2004, and recently revised in February of 2010. The review of such contractual agreements is delegated to a special committee within the MOH, and it may be also be delegated to the Director of the specific institution. The Procedure for Reviewing Contractual Agreements with MOH Medical Institutions and Clalit Health Services 4/10 (2010) (Isr.) is available at http://www.health.gov.il/hozer/mk04_2010.pdf (last visited Sept. 7, 2012).

³⁰² For more information about Clalit Health Services see *supra* note 58. For more information please see the Ministry of Health report, Information in Hospitalization Institutions in Israel *supra* note 284.

³⁰³ See The Procedure for Reviewing Contractual Agreements *supra* note 301 at § 5.4.

³⁰⁴ See the Director General of the Ministry of Health Notice, 14/09 (2009) (Isr.), available at http://www.health.gov.il/hozer/mk14_2009.pdf (last visited Sept. 7, 2012).

risks of COI by all professionals who provide opinions to the MOH by revealing their conflicting interests.³⁰⁵ For a detailed discussion of the COI Guidelines, please refer to Chapter 5.

To assist the MOH with its mission, the MOH uses several statutory advisory committees to obtain expert input on scientific, technical, and policy issues. One such advisory group is the National Ethics Committee.

National Ethics Committee The Public Health Regulations impose mandatory review and approval by the National Ethics Committee when trial applications relate to genetic testing, in vitro fertilization or other circumstances that the MOH sees as requiring further input.³⁰⁶ The Public Health Regulations explicitly impose certain composition and quorum requirements of the National Ethics Committee. Per the Public Health Regulations, this committee should consist of at least ten members: one legal professional; one religious person; six professors from academic institutions, three of whom must be physicians; the Director General of the MOH or its designees, and the head of the Israeli Medical Association.³⁰⁷ According to the MOH official interviewed, in the past, the Director-General assigned his authority to his deputy, and today less senior MOH professionals serve in the National Committee.³⁰⁸

In addition to its scientific and ethical evaluation for specific research proposals, the National Committee follows trends in the area of genetic testing and technologies. In accordance with the Genetic Information Law³⁰⁹, the National Committee must report annually to the Minister of Health regarding its recommendations on how to adjust that law in light of new developments and based on the information stemming from the human genome research project.³¹⁰ The National Committee is generally accountable to the MOH, but they are also accountable to the Ministry of Science and Technology for issues relating to new medical technologies (such as technologies for extracting eggs for fertility or embryonic stem cells research). The Public Health

³⁰⁵ *Id.* at §5.

³⁰⁶ See Public Health Regulations *supra* note 138 at §3B.

³⁰⁷ See *Id.* at appendix 3.

³⁰⁸ Interview with MOH official *supra* note 177.

³⁰⁹ Genetic Information Law, 5761-2000, SH No. 1766 p. 62 (Isr.).

³¹⁰ *Id.*, at §40.

Regulations, the Genetic Information law and the Anti-Cloning law³¹¹ provide the legal framework for the Committee's authority to act as an advisory committee to both ministries.

There is little information published about this National Committee's members, procedures or policies. This committee meets monthly for several hours to review information and make recommendations. Per one of its members, the work of the National Committee is voluntary. Since the National Committee members are all senior professionals working in different facilities, they are not able to meet more than once a month.³¹²

An additional government advisory committee was convened by the MOH to advise it on issues related to gene therapy research applications. As explained by the MOH officials interviewed, within the field of emerging gene therapy, further discussion and analysis on its scientific and ethical merit is required.³¹³

Central Committees In addition to these two special government advisory committees, the Pharmaceutical Administration also uses various Central Committees for further recommendations regarding trial applications not covered under the aforementioned advisory committees' expertise. Per the MOH officials' interviewed, the MOH uses three central committees: a Committee for clinical trials in drugs; a Committee for clinical trials in medical devices; and a Committee for biologic cell and tissue trials. As explained by these officials, these Central Committees are appointed by the MOH to provide their expert input on various scientific issues.³¹⁴

These committees are composed of government employees and outside members. They are generally accountable to the Pharmaceutical Administration as well as the Director-general of the MOH. Unlike National Committee members (but similar to the national advisory committee for gene therapy), the members of these Central Committees are paid for their services at a fixed

³¹¹ See the Prohibition of Genetic Intervention (Human Cloning & Genetic Manipulation of Reproductive Cells) Law, 5759-1999, SH 1697 p. 47 (Isr.).

³¹² Interview with National Committee member, at the office of the member in a hospital, Jerusalem, Israel (September, 11th 2010).

³¹³ Interview with MOH officials, at the MOH offices, Israel (September, 20th 2010).

³¹⁴ *Id.*

price, the funding for which comes directly from the agency's budget. Their workload is variable and each panel is staffed separately.

Scant information is published on the works and process of these Central Committees in Israel. Little information can be found on the MOH website which provides a copy of the procedure of the MOH Central Committee for clinical trials of drugs from October 2000.³¹⁵ These Central Committees are responsible to review and approve the pharmacological and toxicological aspect of the application. Their role is to make sure that the biochemistry of the drug will not be harmful to the participants.

Ad Hoc Experts Lastly, the MOH uses the services of ad hoc experts for their professional input on various scientific and ethical issues. As explained by MOH officials, the MOH may chose to obtain an expert's opinion on a default basis, i.e. where all other existing advisory committees lack the necessary expertise in the area.³¹⁶ Furthermore, the MOH officials specify that all of these Central Committees and appointed experts be comprised of hospital physicians or pharmacists.

The Guidelines for Clinical Trials do not provide any definition or qualifications required of this expert. The interviewed MOH officials indicated that all of these experts are physicians practicing medicine in hospitals.³¹⁷ When the interviewed MOH officials were asked to describe the process for choosing an expert, they explained: "in our every day work, we get to know all the physicians working in the system including MOH employees that work in the field. If there is an application in a certain area, we approach an expert that we know and ask if she or he is willing to issue us with their opinion. Once they accept the offer and issue their opinion, they

³¹⁵Per this procedure, this committee is appointed by the Director-General of the MOH or its deputy for a two year interval. This committee is authorized to review, approve or deny research applications for clinical drugs trials. The committee should consist of at least thirteen members, eight of whom should be physicians (of which one should be a toxicology expert and the other a pharmacology expert) and MOH employees including pharmacist experts.³¹⁵ It should convene at least once every six weeks, and its legal quorum should have at least five members – the chair or its replacement, two physicians, either the toxicology or pharmacology expert and a representative of the Pharmaceutical Administration of the MOH. A copy of the procedure of the activity of the National Committee for Clinical Trials in Drugs, procedure no. 19 (2000) (Isr.) is available at the MOH website at <http://www.health.gov.il/pages/default.asp?maincat=11&catId=301&PageId=2206> (last visited Sept. 7, 2012).

³¹⁶ Interview *supra* note 313.

³¹⁷ *Id.*

receive a fee from the MOH. This money comes from the Pharmaceutical Administration budget...³¹⁸ [Translated from Hebrew]

Hospitals There are many medical institutions conducting research in Israel. These institutions can be distinguished by their source of funding, scope of services and whether or not they are affiliated with academia, acting as teaching hospitals. Based on MOH data, as of 2010, there are a total of 42,119 hospital beds among the different general and specialized medical institutions.³¹⁹ Despite the fact that Israel has several small specialized medical facilities, the vast majority of hospital beds, about ninety percent, are in general hospitals³²⁰ and chronic disease institutions³²¹. Of Israeli's forty-five general hospitals, the government owned hospitals provide the vast majority of the hospital beds, about forty-six percent; Clalit Health Services are second with about thirty percent; while only about three percent is privately owned.³²² Most hospitals have university affiliations and operate training programs for medical students, interns and residents.³²³ For more information about the distribution of hospital beds in general hospitals owned by various entities please refer to Chapter 6.

The national expenditure on hospital services in Israel has been stable since the early 1990s, at about 35 percent of the GDP. Since 2000, the MOH has enabled health plans and hospitals to negotiate directly for lower rate services. As mentioned by Horev et al.,³²⁴ few hospitals offer lower service rates in order to serve a larger stream of patients. At the same time, the health plans' constant pressure to reduce the costs covered under the National Insurance Law has caused hospital management to seek ways to boost revenues.³²⁵ Hospitals began offering services beyond those covered under the National Insurance Law and providing patients with options to

³¹⁸ *Id.*

³¹⁹ See the MOH report *supra* note 302.

³²⁰ The majority of the hospital beds, about 55 percent are in long-term treatment institutions for chronic conditions (mainly geriatric facilities); about 35 percent are in the general hospitals; and about 10 percent are rehabilitation and psychiatry facilities. See the MOH report, Hospital Institutions & Short-term Hospitalizations in Israel (2009) (Isr.), available at <http://www.old.health.gov.il/Download/pages/m050309.pdf> (last visited Sept. 7, 2012).

³²¹ These mainly include geriatric institutions and nursing homes.

³²² See the MOH 2009 report *supra* note 320.

³²³ Israel has four medical schools, each affiliated with general hospitals. They include: the Hebrew University Medical School; the Tel Aviv University Medical School; the Technion Medical School in Haifa and the Ben-Gurion University Medical School in Be'er Sheva.

³²⁴ See Horev & Babad *supra* note 41.

³²⁵ *Id.*

choose their own surgeons (at their own expense). These developments have implications for institutional conflict of interest discussed in subsequent chapters.

Health professionals Physicians play an important role in the Israeli health care system both as owners of clinical knowledge and as holders of executive positions in the health care system. Physicians tend to use their status to promote professional and financial issues, such as the approval of private services in public hospitals. Most physicians are hospital employees and also work for one or more of the health funds.

Particularly pertaining to medical research, the Guidelines for Clinical Trials require that clinical trial investigators or the principal investigator (PI) be “A licensed physician or a licensed dentist who acts as an investigator responsible for the conduct of a clinical trial at a trial site, as defined in the trial protocol”.³²⁶ According to the Declaration of Helsinki, the physician has the duty to: “...promote and safeguard the health of patients.... The physician's knowledge and conscience are dedicated to the fulfillment of this duty.”³²⁷ Based on these defined responsibilities, the PI has a central role in the conduct and supervision of clinical trials, which includes: submitting trial applications, evaluating trial participant conditions and eligibility of trial enrollments, reviewing clinical and laboratory data, and reporting and assessing adverse events.³²⁸ The PI contracts with the trial sponsors to conduct these functions. A copy of the contractual agreements between the trial investigators and the sponsors must be provided to the institutional Helsinki committee for review, and for the government or Clalit-owned hospital to Special Committee of MOH discussed above. Physicians also act as government advisors in the different Central and National Committees discussed above, and they provide crucial scientific and ethical recommendations to the MOH.

Research Sponsor According to the Guidelines for Clinical Trials, the research sponsor is “A person, corporation or institution responsible for the initiation, management, and financing of a clinical trial.”³²⁹ Sponsors are the stakeholders that initiate the research. Typically, they are

³²⁶ See the Guidelines for Clinical Trials *supra* note 35 at §14.

³²⁷ See the Declaration of Helsinki *supra* note 33 at §3.

³²⁸ The PI's regulatory responsibilities are spread out between the Public Health Regulations and Guidelines for Clinical Trials and include §1.2(c), etc.

³²⁹ *Id.*

pharmaceutical or biotechnology companies in the business of making drugs, biologics, or medical devices. They may also be foreign government agencies, such as the U.S. National Institute of Health. Sponsors are engaged in clinical trials in order to ascertain whether their investigational product is safe and effective for commercial use. They hire the research team to conduct the clinical study, but retain the responsibility for submitting research protocols, obtaining insurance coverage for trial-inflicted injuries to participants, supplying the investigational drug to trial participants under certain circumstances for a certain period, and disclosing the contract between the sponsor and the PI to the ethics committee (as discussed below).

According to the U.S. NIH's registry of international clinical trials database, of approximately 3,500 studies conducted in Israel, 53 have a U.S. federal agency (such as the NIH) listed as sponsor; 1,499 studies are sponsored by domestic and foreign biotech companies.³³⁰

Contract Research Organizations (CROs) A CRO is an outsourcing organization appointed by the sponsor that offers a wide range of biomedical research services to assist the sponsor with the clinical trial process.³³¹ Services offered by CROs include: trial management; clinical, medical and safety monitoring; assisting in the preparation of an FDA New Drug Application (NDA); regulatory affairs support and other clinical trial related services. CROs can be large multinational organizations or small specialized entity.

There is very little published information regarding the operation of CROs in Israel. According to information made available online by the Israel Life and Science Industry,³³² five CROs currently operate in Israel. Information is not publically available on how many of these CROs are conducting clinical trials, if any, and under what guidelines. These private corporations, although bound by state law, operate under no specific regulations since the regulatory scheme

³³⁰ See the U.S. National Institute of Health registry's database *supra* note 239.

³³¹ U.S. FDA Regulations define a CRO as follows: "Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration." See 21 CFR 312.3(b).

³³² The Israel Life and Science Industry web-site www.ilsa.org.il/about.asp (last visited Sept. 7, 2012).

refers only to trials conducted in hospitals. Israeli Public Health Regulations do not currently define the responsibilities of CROs.

Institutional Helsinki Committees Each medical institution conducting human trials must have a Helsinki Committee (which is similar to the U.S. IRB). The committee members are appointed by the director of the specific institution with the approval of the MOH.³³³

The Helsinki Committee is defined as “An independent committee whose composition, methods of appointment and legal quorum are defined in the Public Health Regulations.” Its responsibilities entail reviewing all research proposals within the medical facility to ensure regulatory compliance and protection of trial participants throughout the duration of the trial.³³⁴ Specifically Helsinki committees are required to: review and recommend approval of applications for new clinical trials, review and investigate reports regarding serious adverse events, analyze safety reports regarding the investigational product, and review and discuss periodic annual reports from the PI. As described by the head of the Helsinki committee in one of the hospitals: “The Helsinki committee acts as the participant’s guardian, making sure that the patient’s rights are upheld. The assumption is that good research is research that benefits the patient.”³³⁵ [Translated from Hebrew]

To achieve their mission, the Helsinki committees must use their expertise to assess the scientific, ethical and legal legitimacy of every proposed trial protocol. Each Helsinki committee must consist of at least seven members, one of whom must be a legal professional or “religious person,”³³⁶ three of whom must be physicians, and one of whom must represent the institution’s management.³³⁷ As discussed in detail in Chapter 4, as part of the ethical evaluation process, the Helsinki committees are required to review the investigators’ disclosure of their affiliation with the sponsor.³³⁸ These committees are responsible for making sure that no COI exists between the

³³³ See the Public Health Regulations *supra* note 138 at §1, 2nd Appendix.

³³⁴ See §18 of the Guidelines for Clinical Trials *supra* note 35, “Supervision of Clinical Trials;” in high risk trials, investigators are required to submit more frequent reports and report regularly on adverse events.

³³⁵ Interview with hospital 7 official, at the official’s office at the hospital, Israel (September, 21st 2010).

³³⁶ Interestingly, the Public Health Regulations failed to define the term “religious person.”

³³⁷ *Id.*

³³⁸ See § 9 of the Guidelines for Clinical Trials *supra* note 35.

trial investigator and the sponsor.³³⁹ Within its monitoring and supervising role, the Helsinki committee, similar to the U.S. model³⁴⁰, has the authority to withdraw its approval and terminate the trial under certain circumstances.³⁴¹

In summary, the biomedical sector has become a multifaceted arena with complex interactions. The processes, practices and outcomes of such ventures clearly depend on collaboration, partnerships and other affiliations. At the same time, this arena connects stakeholders with different interests and may result in conflicts and tensions. To understand the nature of potential conflicts, which are discussed in detail in Chapters 2 and 4-6, the description of the current infrastructure for the review, approval and oversight of the clinical trial process, is required. Thus, the section below describes Israel's clinical research infrastructure and processes and the key stakeholders' roles therein.

3.5 Israel Clinical Trials Regulatory Approval and Oversight Process

There are many types of clinical trials, which may include preventive, screening, diagnostic or genetics. Trials can be conducted in one site or simultaneously in multiple sites domestically and internationally. Naturally, the design of the clinical trial depends on its type, the number of sites, and its foreseeable risks. Regardless of the specific type of trial or its design, trial objectives aim to advance treatment, diagnosis and disease prevention as well as to understand the etiology and pathogenesis of diseases.³⁴² The sections below distinguish between the review and approval processes and the monitoring and oversight procedures under the current Israeli regime.

Approval Process

Any clinical trial conducted wholly or partly in Israel and involving human subjects must comply with the Public Health Regulations and Guidelines for Clinical Trials. Requirements for the approval process follow:

³³⁹ *Id.* at § 9.2. As discussed in chapter 4, this provision does not provide definition as to what constitute COI.

³⁴⁰ See Angela Bowen, *Models of Institutional Review Board Function in the Oxford Textbook of Clinical Research Ethics*, 556 (Emanuel E. at el. ed. Oxford Uni. Press 2008).

³⁴¹ The Helsinki committee has the authority to decide to discontinue the trial, followed by sending its decision to the sponsor/PI, hospital's management and the MOH. See *Guidelines for Clinical Trials supra* note 35 at § 15.2.3. Furthermore, in case of death to participant, the Helsinki committee is required to immediately investigate the case in order to determine whether or not the death is related to the study. If the committee determines that there is connection, they might require discontinuing the trial. See *Id.* at §15.1.2.1.

³⁴² Clinical trial/study as defined by the *Guidelines for Clinical Trials Id.* at §6.

1. The statutory process begins with the submission of an application for a clinical trial on humans, by a licensed physician or dentist serving as the Principal Investigator (PI) to a medical institution.³⁴³ The application must include: the application form, the trial protocol,³⁴⁴ the investigator's brochure (unless exempt),³⁴⁵ informed consent forms, the sponsor's statement of commitment, a declaration of sponsor or its representative in Israel,³⁴⁶ and a letter to the attending health plan's physician.
2. The medical institution's Helsinki committee reviews the application. Both the Public Health Regulations and Guidelines for Clinical Trials specify different responsibilities for ensuring legal and ethical conduct in research studies depending on the nature of the research, its location, and whether vulnerable participants are used.

The institutional Helsinki committee decides whether the application is for a *Special or Non special Trial*. A *Special Trial* is defined as one that aims to test a medical product for use in Israel that was already accepted by a "recognized country"³⁴⁷ or for purposes not specified on that product's label.³⁴⁸ In the case of products already accepted by a recognized country, the risks are allegedly known, as these products were previously tested. Special Trials can be approved at the institution level.

All other trials are considered to be "*Non Special Trials*" and require the approval of the institution's Helsinki Committee, its Director, and the MOH.³⁴⁹ The decision about whether an application calls for a Special or Non Special Trial is made by the specific institution's Helsinki committee.

³⁴³ *Id.* at §1.2 (c).

³⁴⁴ The Guidelines for Clinical Trials provide a detailed list of items needed in protocols, including: preclinical/clinical information; parameters for evaluations; number of trial participants; study design; and ethical issues pertinent to the trial. See *Id.*, at. §2.2.1.

³⁴⁵ In accordance with the ICH GCP, Guidelines for Clinical Trials required for investigational product, see *Id.* at §2.3.

³⁴⁶ *Id.* at §2.7.

³⁴⁷ A "Recognized Country" is defined in the Definition section of the Guidelines for Clinical Trials; it includes: U.S., E.U., Switzerland, Norway, Iceland, Australia, New Zealand and Japan.

³⁴⁸ *Id.* at §6.

³⁴⁹ See *Id.* at §1.

The Helsinki committee must be provided with a copy of the contractual agreement made between sponsor, PI and other investigators affiliated with the clinical trial. Based on that information, the Director of the institution and/or the MOH must ensure that there is no COI between the researcher and the sponsor.³⁵⁰

3. When trial applications relate to research in areas subject to special oversight review (viz., living cells and tissues, genetic testing, in vitro fertilization), or the Director General of the MOH deems it appropriate, the application is transferred for review and recommendations to the National Ethics Committee.³⁵¹

In other areas of *Non Special Trials*, the MOH can choose from the following three options after receipt and review of the Helsinki Committee's minutes:

- a) Grant an approval;
- b) Refer the application to an expert for review. Should the expert approve the application, the MOH will issue an approval. However, should the expert recommend denying the application, the application is sent to one of the Central Committees for further review.
- c) Refer the application to one of the Central Committees for its recommendation.³⁵²

Figure 3.1 simplifies the approval process for a new application for a clinical trial that involves human subjects according to Israeli Public Health Regulations and Guidelines for Clinical Trials:

³⁵⁰ *Id.* at §9.2.

³⁵¹ See §3B of the Public Health Regulations *supra* note 138.

³⁵² As mentioned above, the Pharmaceutical Administration of the MOH uses various Central Committees for further recommendations regarding trial applications not covered under the aforementioned advisory committees' expertise.

Special/Non-Special Trial Approval Process

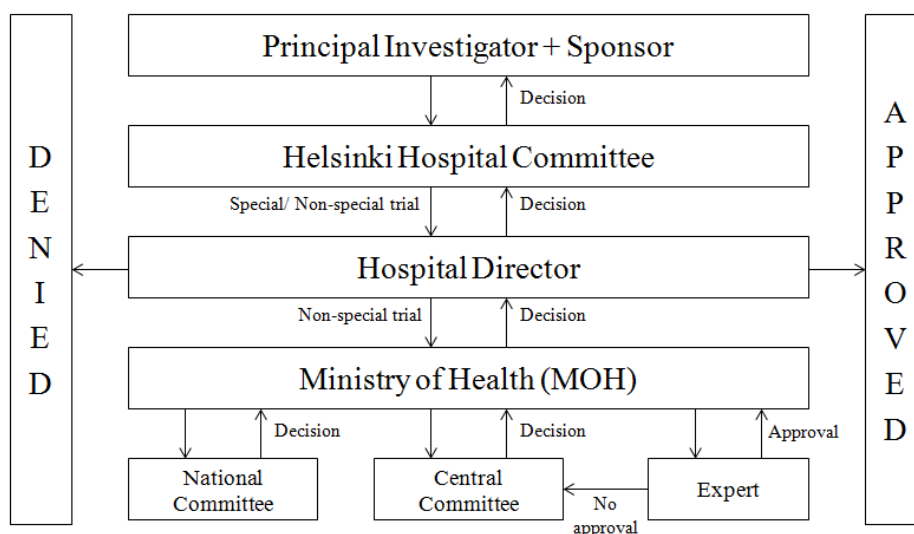


Figure 3.1: Israel's Human Subject Research Approval Process

Neither the Public Health Regulations nor the Guidelines for Clinical Trials provide a specific timeline for the review process and approvals.

4. As mentioned above, the PI and sponsors are responsible for supplying their contractual agreement for review by the MOH Special Committee (only relates to research conducted in hospitals owned by the Government or Clalit Health Services). Upon the approval of these contractual agreements, the application is approved.
5. Once the application is approved, the Guidelines for Clinical Trials provide detailed requirements for reporting duties by the PI, the sponsor, and the medical institutions throughout the duration of the trial, mainly regarding serious adverse events and ongoing safety assessment of the investigational product.³⁵³

Figure 3.2 summarizes the role and responsibilities of the different research reviewers involved in the initial review and approval of research applications within institutions.

³⁵³ See §15 of the Guidelines for Clinical Trials *supra* note 35.

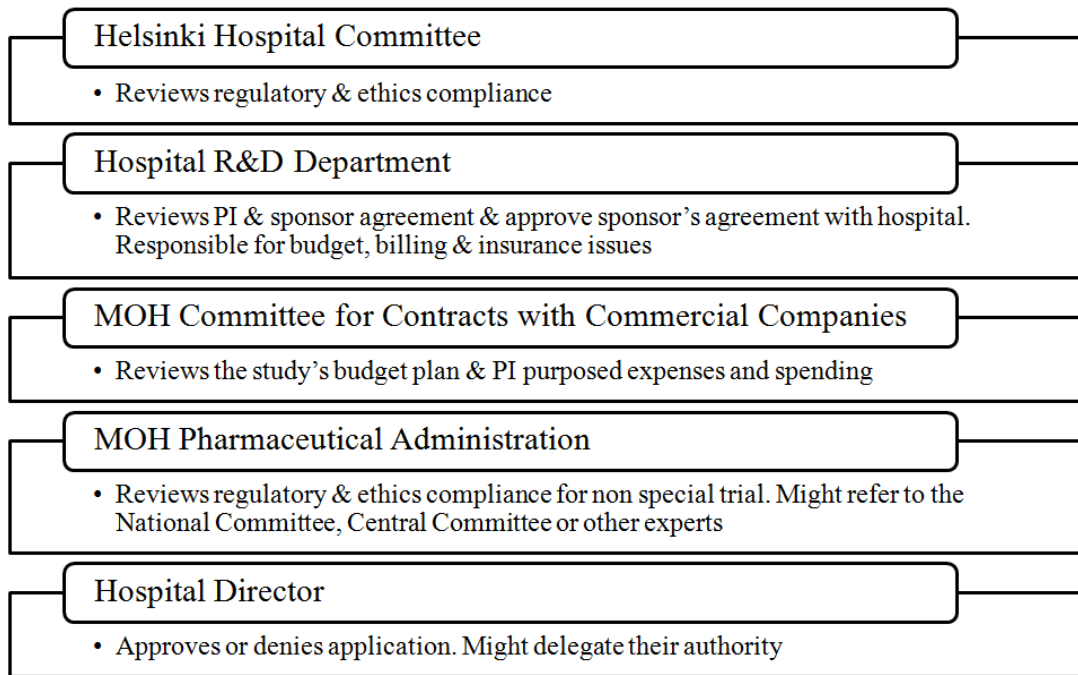


Figure 3.2: The Initial Research Applications Reviewers

Oversight

In addition to reviewing and analyzing trial applications for approval, the Guidelines for Clinical Trials specify additional supervisory duties required of the Helsinki Committees, the management of the medical institutions, and the MOH.

- a) The Helsinki Committee must ensure regulatory compliance and protection of trial participants throughout the duration of the trial.³⁵⁴ They are required to review periodic annual reports from the principal investigators responsible for the trial.³⁵⁵
- b) The medical institution's management or its designee must appoint an audit panel to review and monitor the clinical trials approved at the institution. This audit panel is responsible for oversight to assess compliance with the approved trial plan. It must report every 6 months on its activities and findings to the management of the medical institution and to the Helsinki Committee.³⁵⁶

³⁵⁴ See *Id.* at §18, "Supervision of Clinical Trials;" in high risk trials, investigators are required to submit more frequent reports and report regularly on adverse events.

³⁵⁵ *Id.* at §18.1.

³⁵⁶ *Id.* at §18.2.

- c) The MOH must also conduct oversight via inspections.³⁵⁷ To date, however, no published data has been made available pertaining to the sampled inspections carried out by the MOH.

As this process highlights, the Helsinki Committees, the medical institutions and the MOH play a crucial and central role in safeguarding the rights of human subjects and scientific validity of the research, both by their approval processes and their oversight mechanisms. Consequently, the governance of these stakeholders is critical to ensure effective regulatory and ethical compliance. However, this regulatory framework applies only to research conducted in hospitals and is silent with respect to research conducted in other institutions, such as private labs and CROs.

3.6 Conclusion

Israel has become a world leader in biotechnology research and development. Israel's jurisprudence posits a liberal approach to biomedical research, includes explicit laws, regulations, and guidelines governing research with the aim of protecting the rights of patients and trial participants. The current regulatory scheme is designed to protect the rights of the participants throughout the trial, while the regulatory protection may be extended to a period of up to three years following the trial completion.

Israel's robust growth and innovation in the biomedical sector has an immense importance to the country's economy and hence wields significant political weight. The robust growth of the Israeli clinical research industry has introduced many additional stakeholders and highlighted the existing functions of the both the research institutions and the MOH. These relevant stakeholders range from researchers, sponsors and CROs to academic institutions, hospitals and the MOH. The progress of multi faceted medical research depends on extensive collaboration between these actors, but may result in conflicts and tensions.

Based on the current regulatory infrastructure for the approval and oversight of clinical trials, the medical institutions, particularly the Helsinki Committees, and the MOH play a crucial role in safeguarding the rights of human participants and the scientific validity of research.

³⁵⁷ *Id.* at §18.3.

Consequently, the governance of these key stakeholders is critical to ensure effective regulatory and ethical compliance.

In Chapters 4-6, the approval and oversight infrastructure will be evaluated with respect to risks associated with COI. Based on the literature, Chapters 4-6 will explore three main areas for COI that may affect protection participants' rights or research validity: COI at the individual investigator level, COI at the level of research reviewer, and COI at the research institution level. Chapters 4-6 will be organized to reflect these three main areas of conflicts based on the aforementioned key stakeholders' roles and the current infrastructure.

CHAPTER 4: Conflict of Interest – Researcher

This thesis examines the governance, operations and practices of Israel's biomedical scheme safeguarding against the risks associated with COIs in biomedical research. In five sections, this chapter explores issues of COI ascribed to the individual investigator conducting clinical trials in Israel. It is designed to evaluate whether the current regulatory framework and practices are adequately responding to the risks associated with investigator's COI in Israel. In order to evaluate that, this chapter employs two levels of analysis: conceptual and practical. The conceptual analysis, discussed in section 4.1, describes the tension between on the one side the significant control clinical investigators have over the conduct of the clinical trial, and on the other side the entrepreneurial nature of contemporary medical research. Such tension creates concerns for COI, and asks whether personal conflicting interests can undermine investigator's ethical and scientific responsibilities. This chapter further explores the significant studies published worldwide suggesting that the increasing collaboration with industry has in fact impacted research findings and publications, raising many concerns regarding the validity and objectivity of industry sponsored biomedical research, as well as legal or ethical concerns for individual researchers' misconduct and bias.

The practical analysis, discussed in sections 4.2 and 4.3, portrays the rules, processes and practices in place to address COI at the investigator level. The analysis begins by demonstrating how concerns about investigator financial COI were explicitly addressed by the Israeli regulators through affiliation disclosure requirements and institutional and governmental review processes. Then this chapter proceeds to discuss the information obtained from the interviews conducted with government officials and hospital representatives in charge of the COI review process. Substantial variations were found among the interviewed officials with regard to the interpretation and implementation of the regulatory COI principles. The critique of this chapter, discussed in section 4.4, centers on the practical analysis of the implementation approaches to investigator COI in Israel, showing how these approaches raise a number of research governance practices issues. The following are among the critiques advanced in this chapter: the COI regulatory provision lacks standardized objectives and responsibilities, thus failing to reflect the Israeli scheme's stand on researcher COI; hospitals are implementing limited sources for financial COI assessment; and the current regulatory anomaly of imposing COI review and

approval processes only on certain medical institutions. The last section 4.5 summarizes and concludes the main findings.

4.1 Conceptualizing COI at the Biomedical Researcher Level

The next sections describe the characteristics and regulatory responsibilities of medical researchers and the significant impact they have on critical stages of research. With such extensive discretion over vital stages of the trial in mind, the section to follow discusses emerging worldwide studies suggesting how the increasing collaboration with industry and private funding had impacted these primary responsibilities.

4.1.1 The Israeli Biomedical Researcher: Qualifications and Responsibilities

Any clinical trial involving human subjects conducted in Israel requires the Principal Investigator (“PI”) to submit a clinical trial application.³⁵⁸ Only licensed physicians or licensed dentists can submit clinical trial applications and serve as the trial PI.³⁵⁹ The PI is the head investigator in charge of the actual conduct of the clinical trial. The PI and any sub-investigators³⁶⁰ taking part in research are required to have the “appropriate training” to conduct the trial along with the relevant skills and experience.³⁶¹

An “appropriate training” requires the PI to be trained and to conduct clinical studies, inter alia, in accordance with the International Conference on Harmonization’s (ICH) Good Clinical Practice (GCP) standards.³⁶² These GCP standards are designed to safeguard the trial participants’ safety and rights as well as to ensure the quality and the efficacy of the trial.³⁶³ With the increasing number of clinical studies conducted in Israel over the last two decades by multinational corporations and foreign government agencies, the MOH, hospitals, medical

³⁵⁸ The Guidelines for Clinical Trials provide detailed information of the required application documents which vary in accordance with the nature of the specific trial (whether for drug, medical device, living cells etc). The documents should mainly contain application forms (available online in Hebrew only), research protocol and investigator’s brochure on the investigational drug tested. See Guidelines for Clinical Trials *supra* note 35 at §2.

³⁵⁹ *Id.* at §1.2(c).

³⁶⁰ “Sub-contractor” is defined broadly to include all clinical trial staff appointed and supervised by the PI to perform trial related tasks at the trial site. See *Id.* at §26.

³⁶¹ *Id.* at §1.5.

³⁶² The main goal for the GCP standards was to harmonize the drug approval/registration processes among the U.S., Japan and the E.U. to minimize redundant duplication of testing and other requirements for product registrations by these countries. The ICH GCP *supra* note 52.

³⁶³ Guidelines for Clinical Trials *supra* note 35 at the definition §10.

schools and the Israeli Medical Association (IMA) have now mandate the adoption of these formalized GCP standards in order to be aligned with the accepted international standards.³⁶⁴ Notably, the GCP standards do not define or discuss any processes or practices relating to COI within the conduct of the trial.

Physicians, within their capacity as researchers who conduct clinical trials on human participants, have various responsibilities. These responsibilities include producing a valid scientific study and ensuring participants' safety.³⁶⁵ Their obligation to safeguard the well-being of participants is vital throughout the duration of the trial and includes many critical duties. Among these duties are: adequate recruitment of participants in accordance with the protocol's criteria, monitoring drug interactions, and both treating and reporting any trial- related adverse events. Compliance with the regulatory provisions "is designed to protect the trial participants, ensure that their rights, safety and well-being are maintained, and that the information obtained from the study is reliable."³⁶⁶

Not only are the PI and any other investigators taking part in the trial responsible for safeguarding human participants' health and well-being throughout the duration of the trial, but in Israel these responsibilities can be extended with the approval of the ethics committee even after the trial is already completed. In cases where the PI recommends that the participants' well-being requires continued treatment with the investigational product - as no other appropriate alternative therapy is suitable – such participants will continue to receive the product free of charge up to a period of three years under certain circumstances.³⁶⁷

In addition to the broad fiduciary duties Israeli researchers have toward individual research subjects, they are also responsible for producing a valid scientific study and thus maintaining public trust. The literature acknowledges that the public trust in medical research is built on the

³⁶⁴ Also see Koren *supra* note 49.

³⁶⁵ The primary goals for every biomedical research are "...the generation of new biomedical knowledge in a manner consistent with the rights and interests of any human-research subjects..." See Josephine Johnston, Financial Conflicts of Interest in Biomedical Research, in Trust & Integrity in Biomedical Research 11-12 (Thomas H. Murray & Josephine Johnston ed. John Hopkins 2010).

³⁶⁶ See the General section of the Guidelines for Clinical Trials *supra* note 35.

³⁶⁷ *Id.* at §17. These Guidelines provide both the PI and the trial sponsor the right to appeal the ethics committee's decision regarding the continued treatment with the investigational drug. See *Id.* at §17.2.

assumption that science is carried out with scholarly integrity and independence.³⁶⁸ The responsibility to maintain public trust and to create valid publications was fundamentally extended by the judicial branch in Israel to both the research community as well as society at large. As discussed in Chapter 2, the *Dicker* case illustrates such extended investigator fiduciary duties. The Israeli court, in the *Dicker* case, recognized senior physician-researcher's responsibility not only toward any potential patients (to be treated with an alleged tested therapeutic), but also toward other physicians and medical journals.³⁶⁹ The main concern raised by the court was the fact that fictitious and invalid research findings can create harmful clinical practices impacting broad public interests.

In sum, the Israeli regulatory scheme imposes critical responsibilities upon skilled medical researchers taking part in clinical trials involving human subjects. Two primary goals are emphasized by the current regime to include the protection of the human participants and the construction of valid research results. These primary goals have been interpreted broadly by the regulatory scheme and the judicial branch, extending the boundaries of responsibility beyond the trial period and beyond the scope of the particular participants to the public as a whole.

4.1.2 Investigator COI Challenges Objectivity

Regulatory responsibilities and obligations imposed on trial investigators directly correlate with investigator's crucial role. Briefly, every clinical trial involving human participants comprises key decision-making steps: determining study design, objectives and methods, conducting the trial, analyzing and interpreting data, and reporting findings. The degree of the investigators' decision-making in all parts of the research processes is extensive.³⁷⁰

With so many aspects of research process at the discretion of the PI, one cannot emphasize enough the importance of scientific objectivity in clinical trials. There is no doubt that scientific objectivity and research integrity are key goals in the conduct of clinical trials. Per Krimsky, successful professionalism in clinical studies necessitates "...unfettered commitment to

³⁶⁸ See for example Du Val *supra* note 11.

³⁶⁹ See *Dicker* case *supra* note 38.

³⁷⁰ See generally the IOM report *supra* note 32.

methodological rigor and the pursuit of verifiable knowledge.”³⁷¹ Lemmens views the role of trial investigator as a privilege to be accompanied by a commitment to society. He further interprets such professional commitment as being to “conduct research with integrity and with the commitment to search for truth.”³⁷² Essentially, every decision-making process can potentially be skewed. Specifically within the conduct of medical study, Shamoo and Resnik argue that some areas of research are more susceptible to COI, such as deciding on study questions, selecting a research design, analyzing and interpreting data, as well as selecting and recruiting subjects.³⁷³ They explain that having conflicting interests can affect thought processes and behavior which can undermine objectivity.³⁷⁴

As defined earlier, COI arises when professional judgment or action concerning primary interest will be overly influenced by a secondary interest.³⁷⁵ As discussed above in section 4.1.1, the investigators’ primary interests and duties include safeguarding the participants’ health and wellbeing, producing scientifically valid research, and maintaining the public trust.³⁷⁶ Secondary interests may include non-financial and financial incentives resulting from collaboration with industry, or other personal interests, which are more fully described below. The main concern is whether the investigator’s conflicting personal interests can undermine his or her responsibilities to maintain his or her primary duties.³⁷⁷ COI can create bias in researchers’ decision-making practices and potentially jeopardize the safety of research participants and the validity of the research.³⁷⁸

There are various types of secondary conflicting interests which may affect the researcher’s primary duties. The literature describes two main types of conflicted secondary interests – financial and non-financial.

³⁷¹ See Krinsky *supra* note 73 at 64.

³⁷² See Lemmens *supra* note 29 at 752.

³⁷³ See Shamoo & Resnik *supra* note 14 at 192.

³⁷⁴ *Id.* at 189.

³⁷⁵ See Thompson *supra* note 34 at 573-576.

³⁷⁶ *Id.*

³⁷⁷ *Id.*

³⁷⁸ See Gatter *supra* note 27.

- Financial COI – an example of a secondary interest is investigators’ aspirations to generate revenues or gain personally from their conduct of the trial.³⁷⁹ Lemmens provides few excellent examples for financial incentives, such as clinicians and researchers being tempted to recruit their patients into clinical trials only to receive recruitment fees from sponsors; or researchers being rewarded by pharmaceutical companies for serving as consultants or experts with an explicit or inexplicit expectation of successful trial results.³⁸⁰

These types of financial interests have become evident in light of heavy funding of the majority of biomedical research by private industry. Strong collaboration with industry has created strong alliances and financial interests for physicians-researchers working in public nonprofit research institutions.³⁸¹ Notwithstanding the strong ties with industry sponsors, individual researchers have been increasingly seeking to enhance their own financial interests in the studies they conduct. Sponsor allegiances and individual investment have introduced powerful financial incentives to ensure the success of an investigator’s study.³⁸² The competitive and profit-driven nature of the life science industry – according to some analysts³⁸³ – has become a threat to the scientific paradigm of objective inquiry and free dissemination of knowledge. The concern is that conflicted researchers motivated by financial personal gain, will make biased decisions which may jeopardize the protection of research participants and the scientific validity of their research.

- Non-Financial interests – Researchers may also have other intrinsic interests³⁸⁴, such as aspirations for academic advancement, heightened reputation for pursuing scientific knowledge, and publication. By virtue of conducting medical studies, a potential conflict already exists due to the dual role that physicians-investigators play. On the one side, they have the duty to pursue scientific knowledge to benefit society, and on the other they are

³⁷⁹ One example described by the literature describes a situation where the investigator inflating the trial costs to generate a surplus for other researches to pursue. For more examples, see Ferris & Naylor *supra* note 44 at 118.

³⁸⁰ See Lemmens *supra* note 29 at 752.

³⁸¹ See Beauchamp & Childress *supra* note 10 at 12.

³⁸² See Du Val *supra* note 11.

³⁸³ For example, see Kubiak *supra* note 12.

³⁸⁴ *Id.*

obligated to safeguard the wellbeing of their patients and clinical trial participants.³⁸⁵ In fact, this profound conflict was the reason why U.S. federal agencies in the 1970s insisted on establishing independent evaluations by ethics committees.³⁸⁶

As discussed in Chapter 2, the Israeli and the U.S. regimes mostly address concerns relating to the effects of researchers' financial COI and not other intrinsic non-financial interests. Thompson explains that such focus should be attributed to the fact that financial benefits are easier to regulate by objective rules.³⁸⁷ Emanuel and Thompson add that financial interests are typically considered in the literature as to be prohibited as secondary interests, as opposed to other interests whose prohibition is heavily debated.³⁸⁸ COI are not considered good nor bad, but their presence can interfere with the perceptions (whether the public, colleagues, institutions etc) of a scientist's integrity and independence.

To date, there is no consensus among research institutions worldwide on how to respond to researcher's financial COI, although most institutions have adopted some kind of financial COI disclosure policies. As discussed in detail below, the Israeli hospitals described different approaches to addressing investigator's COI risks, which parallel the diverse strategies taken by institutions worldwide.

In sum, trial investigators in Israel have extensive decision-making responsibilities on critical stages of research. With such extensive discretion over vital stages of the trial, it is not surprising that a high level of scientific objectivity and integrity was recognized in the literature as imperative. Investigator COI has the potential to affect the investigators' mindset and motivation, ultimately disrupting their primary duties.³⁸⁹ The conflicting secondary interests are typically divided into two types: financial and non-financial. Despite the fact that both types of secondary interests can be equally harmful to objectivity, the COI rules in the U.S. and Israel only address the concerns of financial COI.

³⁸⁵ The U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in addressed this inherent conflict in their 1978 report. See *supra* note 28.

³⁸⁶ See Lemmens *supra* note 29.

³⁸⁷ See Thompson *supra* note 34 at 291.

³⁸⁸ Emanuel & Thompson *supra* note 26 at 760.

³⁸⁹ Gatter *supra* note 27.

4.1.3 Empirical Data Published in the U.S. On Researcher COI

In the U.S. concerns about physician bias or COI in view of their close relations with the biomedical industry are certainly not new. Thompson argues that the 1980s marked a shift to an era in which medical literature began to seriously address various areas of COI in physicians' practices.³⁹⁰ Thompson explains that contrary to other professions³⁹¹, the concerns for COI in the medical profession were never formally addressed before the 1980s.³⁹² These concerns were initially raised in the literature with respect to physicians' medical practices within their capacity as both clinicians and researchers: physician self-referral practices, physician risk-sharing in HMOs and hospitals, physician conduct of industry-sponsored research, and research on their own patients.³⁹³

Certainly, the worldwide concerns for risks associated with COI resulting from the relations between the biomedical industry and physicians were not bestowed only on medical research. Much of the scholarship initially focused on potential COI within the physicians' medical practices. According to Marc Rodwin³⁹⁴, for example, it is customary in the U.S., Japan and France that the pharmaceutical and medical device industry use gifts and grants to influence physicians' prescription choices to boost their sales. In the U.S., for example, several institutional heads (including Harvard Medical School, the Institute on Medicine and the Association of American Medical Colleges) protested against the ongoing marketing strategies by pharmaceutical and medical device companies promoting sales through targeting of individual physicians.³⁹⁵ They argue that approximately 90 percent of the 21 billion USD marketing budget of the pharmaceutical industry continues to be directed at physicians.³⁹⁶ According to David Korn, former dean of Stanford medical school and former AAMC Chief

³⁹⁰ See Thompson *supra* note 34.

³⁹¹ Many professions have been developing COI theories and policies for many years addressing circumstance where the professional's objectives collide with the professionals' self-interest. Economic literature, for example, has discussed the agency problems and auditor independence requirements. For more information regarding the challenges of COI in different areas of business, law and public policy see Don A. Moore et al. ed., *Conflict of interest: Challenges & Solutions in Business, Law, Medicine, and Public Policy*, (Cambridge 2005).

³⁹² See Thompson *supra* note 34.

³⁹³ *Id.* at 290.

³⁹⁴ Rodwin *supra* note 19.

³⁹⁵ Troyen A. Brennan et al., *Health Industry Practices that Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers*, 295 *JAMA* 429 (2006).

³⁹⁶ *Id.*

Scientific Officer, physicians accepting billions of dollars in gifts, meals, paid travel, etc, had become “so embedded in the medical profession”³⁹⁷, creating fundamental financial COI.³⁹⁸ These mentioned institutional heads called for eliminating those financial incentives from the medical profession starting from medical schools educating future generation of physicians.³⁹⁹

The Israeli Medical Association (IMA) addressed these alleged ‘embedded’ practices in its code of ethics, calling on physicians to refrain from accepting gifts from commercial companies or taking part in marketing or selling products on behalf of for-profit companies.⁴⁰⁰ The potential COI resulting from the relations between the biomedical industry and physicians was also addressed by the Israeli legislature. As discussed in Chapter 2, in 2008 and later in 2010, rigorous statutory disclosure provision was enacted.⁴⁰¹ This statute imposes disclosure provisions, inter alia, on public physicians and researchers focusing on the appropriateness of donations paid by the biomedical industry.⁴⁰²

Rodwin frames the “heart of the matter” for individual physician COI as the tension between physicians’ self-interest and their fiduciary obligations to their patients and to the public as a whole.⁴⁰³ He argues that the risk of physicians’ misconduct (such as prescribing more tests or therapies that patients do not necessarily need in order to get more reimbursement from the insurance) intensifies as the financial incentives increase.⁴⁰⁴

Particularly within medical research, a robust empirical and scholarly study conducted in the last two decades has indicated that financial COI has been associated with a number of concerning research practices. These studies have shown, inter alia, increased likelihood of pro-industry findings, withholding negative results from publication, restricting investigator’s publication, and

³⁹⁷ David Korn, M.D., Financial Conflicts of Interest in Academic Medicine: Whence They Came, Where They Went, 8 Ind. Health L. Rev. 1 (2010).

³⁹⁸ See Troyen A. Brennan et al. *supra* note 395.

³⁹⁹ *Id.*

⁴⁰⁰ Physicians, who failed to comply with the provisions of this code of ethics, might be subject to disciplinary proceedings which may result in cancellation of membership. IMA’s Code of Ethics *supra* note 123.

⁴⁰¹ See *supra* note 188.

⁴⁰² With regard to physicians, the threshold for disclosure is annual donations of more than 2,500 NIS.

⁴⁰³ See Rodwin *supra* note 19 at 7-9.

⁴⁰⁴ *Id.* at 16.

implementing biased study designs.⁴⁰⁵ Below are some of the many examples from the last decades' literature, illustrating the core challenges resulting from the strong ties between investigators working in public non-profit institutions and private corporations.

Considerable studies published in various medical journals showed that a privately sponsored study will more likely favor the sponsor's product, as oppose to a similar study funded by a non-profit or government agency. Friedberg et al. (1999) found that 95 percent of industry-sponsored articles on cancer treatment drugs stated positive outcomes, as oppose to 62 percent of non-industry sponsored articles.⁴⁰⁶ Ridker and Torres (2006) analyzed 349 consecutive randomized clinical trials for new cardiovascular drugs published in the major medical journals between 2000 and 2005. They reported that 67 percent of the trials sponsored by the industry supported the new treatment over the standard of care; whereas only 49 percent of the not-for-profit funded trials supported it (51 percent of the not-for-profit institutions in fact favored the current standard of care over the new drug).⁴⁰⁷ Another interesting study mentioned was the analysis of articles testing the health effects of passive smoking. These studies found that 94 percent of the reviews conducted by tobacco-affiliated authors reported that passive smoking is not harmful, whereas only 18 percent of the non-tobacco-affiliated supported that conclusion.⁴⁰⁸

Another well publicized study had suggested a troubling number of researchers who admitted to falsifying and/or altering research findings. A 2005 study surveyed more than 3,000 U.S. scientists receiving funding by the U.S. NIH.⁴⁰⁹ They reported striking information regarding a regular misbehavior of scientists in variety of questionable research practices. Even though investigators indicated some questionable practices when conducting research, the largest number of scientists – 15.5 percent -- admitted to having changed research design, methodology or outcome due to external pressure imposed by the trial sponsor.⁴¹⁰ The study, however, does

⁴⁰⁵ See Okike et al. *supra* note 13.

⁴⁰⁶ Cited in Shamoo & Resnik *supra* note 14.

⁴⁰⁷ Paul M. Ridker & Jose Torres, Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations: 2000-2005, *JAMA*. 2006; 295(19): 2270-2274.

⁴⁰⁸ See Lindsay A. Hampson et al., Empirical Data on Conflict of Interest, in *The Oxford Textbook of Clinical Research Ethics*, 676 (Emanuel et al. ed. Oxford 2008).

⁴⁰⁹ Martinson, Anderson & De Vries, *Nature: International Weekly Journal of Science*, 435 Issue 7043, 737 (2005).

⁴¹⁰ Other questionable research practices included: 10.8 percent admitted to withholding details of methodology or results in papers or proposals; 13.5 percent admitted using inadequate or inappropriate research design. Arguably, investigators' self reporting on their misbehavior in antonymic survey is questionable. *Id.*

not provide further information explaining the type of pressure indicated by the scientists to have had impacted their decision-making, nor the areas of practices of the surveyed scientists.

Other studies indicate that private funding has been impacting the conclusions of peer-reviewed publications and media reports. They show a biased trend in reporting negative outcomes in industry sponsored trials.⁴¹¹ Moreover, although clinical trials can measure numerous outcomes and endpoints, some studies suggest that researchers are more likely to choose to publish those conclusions indicating positive outcomes.⁴¹² A more recent study found that key authors in oncology drug or biologic trials are more likely to have financial ties to industry than none key authors.⁴¹³ The study found that these “key authors” with financial ties to the industry, are the ones that are in fact in charge of the vital steps of the trials from the conception, design and analysis to the interpretation or reporting.⁴¹⁴

Notwithstanding the ties with industry sponsors, a different set of studies show that researchers have been increasing their own financial interests in the studies they conduct. More and more investigators, when they discover and develop new therapeutics with commercial potential, seek personal financial rewards. A study of biomedical researchers in the U.S. found that about 22 percent had applied for patents within the last few years, and 25 percent participated in corporate pursuit.⁴¹⁵ Another study suggests that one fifth of about 2,000 science faculty surveyed in the U.S. have reported delaying publication for more than six months to protect intellectual rights of the investigated product (either for finalizing patent application or IP related dispute) or to delay the distribution of negative trial results.⁴¹⁶ These delays were associated with author and researchers’ ties with the industry-sponsor and/or with their engagement in their own commercial activities.⁴¹⁷

⁴¹¹ See T. Caulfield, E. Einsiedel, JF. Merz & D. Nicol, Trust, Patents and Public Perceptions: the Governance of Controversial Biotechnology Research, *Nature biotechnology* 24, 11 (2006).

⁴¹² See Du Val *supra* note 11.

⁴¹³ Rose; Krzyzanowska & Joffe, Relationships Between Authorship Contributions and Author’s Industry Financial Ties Among Oncology Clinical Trials, *Journal of Clinical Oncology*, 28, 8, 1316-1321 (2010).

⁴¹⁴ *Id.*

⁴¹⁵ Bouchard *supra* note 15.

⁴¹⁶ See Hampson et al. *supra* note 408 at 772.

⁴¹⁷ *Id.*

In sum, emerging studies have demonstrated that there is increasingly available support for research by the private sector and close collaboration between for-profit corporations and individual researchers worldwide. Data suggest that the increasing collaboration with industry and private funding had impacted research findings and publications. Moreover, additional studies show that individual investigators have been increasingly pursuing profit and commercial avenues along with their research and development work.

Shamoo and Resnik argue that a plausible reason for the demonstrated correlation between sources of funding and research outcomes is that financial interests have biased the judgments and decisions made by investigators.⁴¹⁸ These findings have raised many concerns regarding the validity and objectivity of industry sponsored biomedical research, as well as legal or ethical concerns for individual researchers' misconduct and bias. This literature is growing, and it is disturbing.

4.1.4 What About Israeli Investigators' Financial COI?

Currently, it is difficult to assess how much clinical research in Israel is funded by industry as there are no published data. Partial data are published regarding the amount of funding provided by industry for research in state owned hospitals and hospitals owned by the Clalit Health Services.⁴¹⁹ MOH data reveal that in these hospitals, in 2009 and 2010 the private biomedical sector invested approximately eighty million dollars⁴²⁰ in clinical trials in Israel. In accordance with interview data, the vast majority, 60-80 percent, of drug trials in Israel are sponsored by commercial industry, whereas for non-drug trials (such as medical devices) only about 10 percent.⁴²¹

Generally, conducting clinical trials on behalf of a commercial sponsor requires collaboration between sponsors and clinicians working with patients on whom the investigational agent can be tested. In Israel data regarding the nature of these collaborations are scarce. Based on interviews conducted with hospital and MOH officials in Israel, it appears that customarily the pre-approval

⁴¹⁸ See Shamoo & Resnik *supra* note 14 at 189-190.

⁴¹⁹ For more information about Clalit Health Services, see *supra* note 58.

⁴²⁰ See the Marker report *supra* note 9. Notably, other publicly and privately hospitals, are not required to provide data regarding research funding to the MOH.

⁴²¹ Interview with MOH officials *supra* note 313.

interactions initially start directly between the sponsor (whether a domestic company, international corporation or governmental agency) and the specific physician-investigator working in a hospital.⁴²² The sponsor begins by offering the investigator the role of PI, testing the former product on eligible participants.⁴²³ Once the initial negotiations are successful, the clinical investigator links the sponsor with his or her employer – the hospital – to finalize the contractual research agreement between the sponsor, the investigator and the hospital. Upon the approval of the trial, part of the research budget is allocated to the hospital and investigators' fee.⁴²⁴ Such collaboration with the biomedical industry provides an important source of revenue for both public hospitals⁴²⁵ and researchers.

Data regarding average monthly incomes of physicians working at state owned hospitals are published by the Ministry of Finance. Information regarding the income of physicians working for other public or private institutions is not available. As of 2007, the average gross annual income of a specialist physician working in a state hospital is about NIS 227,316 (~56,829 USD), and a senior physician NIS 327,312 (~ 81,828 USD).⁴²⁶ To this base salary, other elements are typically added depending on the additional activities the physician is undertaking, including administrating clinical research and/or working for a private industry or HMO.⁴²⁷ The additional average annual income from research activities was indicated in the article as NIS 192,294 (~48,073 USD) for senior physicians and NIS 53,328 (13,332 USD) for specialists.⁴²⁸ Based on this information it seems that on average, senior physicians taking part in research activities earn an additional 58 percent above their salaries and for the specialist an additional of 23 percent. With such surplus earnings, it seems fairly reasonable to argue that at least for

⁴²² According to MOH official, the process typically begins with the negotiations between the researcher and the sponsor. See interview with MOH official *supra* note 185.

⁴²³ This pre-approval model is also customary in the U.S. and Canada, for more information see the U.S. FDA, Sponsor - Investigator - IRB Interrelationship - Information Sheet Guidance for Institutional Review Boards and Clinical Investigators updated in 10.18.10, available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126425.htm> (last visited Sept. 7, 2012).

⁴²⁴ Interview *supra* note 185.

⁴²⁵ The revenues generated by clinical trials from the industry contributed to the hospitals' operations including the ability to obtain advanced medical equipment.

⁴²⁶ These amounts are base-gross income for seniors and specialists' physicians working in government owned hospitals. See Ran Resnik, The Ministry of Finance: The Senior and Specialist Physicians' average [monthly] income amounts to NIS 50-85 thousand (Misrad Haotzar: Hasachar hamemotzah shel rofeem bechirim ve momchim megeaa le 50-85 elef shekel bechodesh bememotzah), (5.27.07) available at <http://www.themarket.com/career/1.445218> (last visited Sept. 7, 2012).

⁴²⁷ *Id.*

⁴²⁸ *Id.*

physicians working at state owned hospitals, undertaking research activities provides an important source of income.

Another source of information shedding some light on the relations between public physicians and the biomedical industry has been gathered by the MOH. An unpublished MOH report reveals the amount of industry-sponsored research trials governed by each PI (hospital-investigator) working for state or Clalit owned hospitals in the years 2006 to 2009.⁴²⁹ It stipulates, for example, that in 2009 a certain investigator from the Soroka University Medical Center proposed the largest industry sponsored research budget in 2009 for the total amount of ~NIS 14.3 million (approximately 3.57 million USD) for two research applications. The second and third in 2009 were investigators from Rambam Medical Center and Tel Aviv Sourasky Medical Center respectively for a total amount of ~NIS 8.8/8.2 million (approximately 2.2/2.05 million USD) for 3 and 7 research applications.

Based on the mentioned MOH data, in 2009 out of total number of 530 the researchers reviewed, more than 13 percent submitted applications for commercially sponsored trials of more than NIS 1 million (~250,000 USD) each; more than 16 percent of the researchers submitted applications for between NIS 500,000 and NIS 1 million (~125,000 - 250,000 USD) each; and more that 42 percent for NIS 100,000 – 500,000 (~25,000 - 125,000 USD). These data also show that the funding for clinical trials by industry has been increasing from the years 2006 to 2009. The figure 4.1 below presents the industry's investment in clinical research in the years 2006-2009 in million NIS.⁴³⁰

⁴²⁹ See the MOH's Committee for Contracts with Commercial Companies, Medical Research Conducted by Investigators during 2009 Compared to 2006-2009 (In NIS), (September 6, 2010) [Hebrew] (unpublished report) (on file with Author).

⁴³⁰ *Id.*

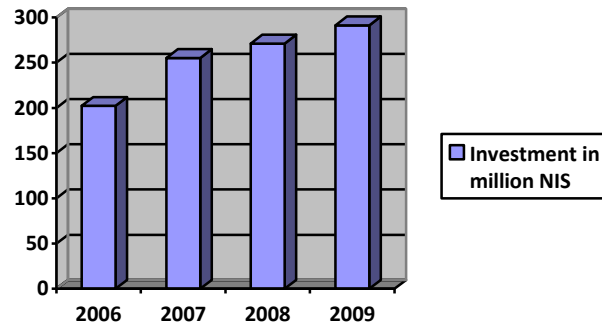


Figure 4.1: Industry Investments in Clinical Trials in Israel 2006-2009

Even though these numbers do not indicate any correlation between the research budget and the investigator's personal income, comparing these numbers to physicians' average annual income may indicate how important these studies are to these researchers.

The concern of potential COI resulting from investigators working in public non-profit institutions' strong ties with industry are not theoretical. In fact, close collaboration was explicitly acknowledged by the Israeli legislature as a serious enough concern to merit continuous review and oversight by the MOH.⁴³¹ However, these concerns were not supported by empirical data suggesting negative impact and biases, but rather were levied to point out that the annual national healthcare spending on drugs and medical devices is increasing.⁴³²

4.1.5 What About Non-Financial Interests?

For medical scientists working in public non-profit institutions, often times the conflicting interests may not be primarily financial. Many of these personal interests are associated with professional aspirations, including pursuit for reputation, funding, tenure, and promotions.⁴³³ In fact, scientists may be zealous about their work, looking to take part in scientific advancement for the sake of the public. Good examples for these aspirations, not predominantly financial, may include: desire for faculty and professional advancement, securing sponsored research funding,

⁴³¹ The National Health Insurance Law §40A 5723-1994 [1995] (Isr.)

⁴³² The main purpose for enacting the new disclosure act was to provide the MOH with an effective tool to manage COI in areas of health. See the introduction to §29 of chapter 7 of the Arrangement Law 2010 available at <http://www.shituf.gov.il/discussion/285> (last visited Sept. 7, 2012).

⁴³³ See Shamoo & Resnik *supra* note 14 at 192.

receiving professional recognition from peers and attaining esteemed research related prizes. Analysts believe that these nonfinancial forces may generate conflicts by creating strong bias influencing thoughts and behavior processes.⁴³⁴ In Israel, the majority of the interviewees, as discussed below, believe that particularly in Israel incentive for professional advancement is in fact the most enduring pressure of all. Such pressure is directly resulting from the criteria for professional advancement. Professional advancement for physicians working for public institutions requires meeting defined criteria for a minimum number of research publications. In Israel the pressure to publish in Israel is extensive⁴³⁵, as physicians cannot secure tenure or administrative positions within the hospitals without it. One hospital official interviewed⁴³⁶ went on to speculate that the pressure to publish was the main reason causing Dr. Dicker to forge his fictitious research paper.⁴³⁷

As some of the interviewees believe, this aspiration for professional advancement is much more powerful from any relations with commercial sponsors. As one interviewee indicated: “I think that publishing an article in “Nature” is much more important than money. For academic or hospital researcher the professional advancement is much more central than money.”⁴³⁸ [Translated from Hebrew] However, despite this strong impact of these non-financial interests on Israeli investigators, most of the regulatory attention has actually been put on the financial COI. A reasonable explanation for that might be because it is practically easier to identify and measure financial COI as opposed to nonfinancial interests. Another explanation is because nonfinancial interests are mostly considered legitimate and even desirable professional practices.⁴³⁹

The great deal of concern for potential financial COI, particularly within the public office setting, has resulted in the implementation of a number of safeguards both at the institutional and at the government levels in many countries including Israel. With the increasing financial incentives to

⁴³⁴ David Korn argues that these nonfinancial incentives may in fact be more powerful pressure to impact researchers’ mindset and motivation, than the pure financial incentives. However, he notes that these pressures are for the most part rarely reviewed by the institutions for potential COI. See David Korn *supra* note 397.

⁴³⁵ Interview with National Committee member, in Jerusalem, Israel (September 19th, 2010).

⁴³⁶ Interview with hospital 2 official, at the official’s office at hospital 2, Israel (August 31st, 2010).

⁴³⁷ As discussed in chapter 2, Dr. Dicker was convicted in 2009 for committing among other offenses a breach of trust. Dr. Dicker, was convicted to have issued an article for publication based on fictitious clinical research.

⁴³⁸ Interview with National Committee member, in Jerusalem, Israel (September 19th, 2010).

⁴³⁹ These legitimate secondary interests may include scientific recognition and grant support. See Emanuel & Thompson *supra* note 26.

physicians working for public nonprofit institutions, there has been a public demand to increase scrutiny. The section below explores the regulatory methods currently in existence in Israel responding to these financial COI concerns.

4.2 Managing Investigator COI under the Israeli Regime – Regulatory Mechanisms

Rather than restricting the commercial funding of research activities and/or other professional activities, the Israeli regulatory scheme chose to ensure continued commercial funding but with oversight. The next sections explore the Israeli regulatory mechanisms in place to address the concerns of COI arising from researchers' collaborations with commercial sponsors. These mechanisms employ two main procedural processes: (1) self-reporting disclosure followed by institutional review, and (2) oversight of financial ties prior to the inception of the trial.

Physicians working for state owned hospitals are subject to an additional regulatory mechanism, discussed below, that restricts their private engagements outside the hospitals.

4.2.1 Researchers' Affiliation Disclosure and Institutional Review

On the face of it, the regulatory scheme provides a simple COI review process instigated at the institutional level. The COI review begins with the researcher's disclosure of any "affiliation" to a commercial sponsor as part of the trial application form submitted to the hospital.⁴⁴⁰ Affiliation is defined broadly as: "A relationship of paid employment; or commercial or business relationship; or family or personal relationship; or any other relationship, including a subordinate work relationship, which could be construed as a conflict of interest or dependence; except for reimbursement of expenditures or remuneration for participation in committees..."⁴⁴¹

Hospital officials, mainly the Helsinki committee⁴⁴² and the director, are required to review this form and, based on the disclosed information, evaluate whether a COI exists. The hospital director "**...must ensure that there is no conflict of interest in conducting the trial** at the medical institution between the commercial company and the Investigator, employee of the

⁴⁴⁰ This is the MOH required form, in Hebrew, used by all the hospital in Israel. The forms are available in Hebrew at the MOH website at <http://www.old.health.gov.il/pages/default.asp?maincat=11&catid=301&pageid=2206> (last visited Sept. 7, 2012).

⁴⁴¹ The Guideline for Clinical Trials *supra* note 35 at §2 Definition chapter.

⁴⁴² The Guidelines for Clinical Trials requires the Helsinki committee to review and approve all the clinical trial applications. *Id.*, at §1.2.

medical institution.”⁴⁴³ [Emphasis by the Author] Apparently, the regulatory scheme prohibits any COI resulting from the researcher-sponsor affiliation, and imposes an obligation upon the institution to enforce it. Surprisingly and significantly, the Guidelines for Clinical Trials do not define what constitutes such prohibited COI, nor do they provide clear standards to hospitals on how to eliminate or manage COI. These regulatory gaps can cause what Thompson calls a “deficiency in disclosure”, i.e. undesired circumstances where those who review the disclosed affiliation information may not know how to interpret it.⁴⁴⁴ For example, does the COI provision take the stance that any affiliation constitutes COI or just certain affiliations?

Implementation of such a broad and unspecified regulatory provision can only be understood by interviewing the stakeholders involved in the COI review process. Consequently, the next section 4.3 will discuss data derived from interviews with relevant stakeholders.

4.2.2 Regulating Financial Ties with Sponsors – Hospitals and MOH

In addition to the disclosure and review mechanism, the Israeli regime also imposes pre-approval review of the contractual agreement and any remuneration offered to the individual researcher by the sponsor directly or indirectly related to the trial.⁴⁴⁵ The hospital director or its designee, typically the R&D department, is authorized to review and approve these financial obligations before the inception of the trial.⁴⁴⁶

For state owned hospitals or hospitals owned by Clalit, additional review is required by the MOH’s ‘Committee for Contracts with Commercial Companies’ (“MOH Special Committee”). This MOH Special Committee reviews the relation between the proposed budget plan for the trial and the commitments and responsibilities of that trial. This committee also reviews and approves payments made by the industry for any travel expenses for conferences, continued medical education and other professional activities. A representative of this MOH Special Committee clarified that there is a computerized mathematical formula for trial budget expenses

⁴⁴³ *Id.* at §9.2.

⁴⁴⁴ Thompson regards this deficiency with regard to trial participants and not the regulatory reviewers. In his mind, such affiliation information may cause confusion and anxiety among the trial subjects. See Thompson *supra* note 34 at 295-297.

⁴⁴⁵ See Guidelines for Clinical Trials *supra* note 35 at §9.

⁴⁴⁶ *Id.*

and a fee cap determined based on the physician or staff's seniority. If the proposed trial budget largely deviates from that cap, then further review is warranted. If the expenses look reasonable, then the MOH Special Committee will approve it.⁴⁴⁷ This representative also clarified that: "the MOH Special Committee motto is to approve the research and not to try and stop it. These researches help promoting the scientific knowledge, and also help promoting our professionals researchers."⁴⁴⁸ [Translated from Hebrew] For the five biggest state hospitals, the MOH Special Committee has delegated its approval process to the hospitals themselves for trial plans budgeted below 100,000 USD.⁴⁴⁹ The MOH Special Committee offers its review services to all hospitals in Israel, not only to state and Clalit owned, however only one has shown any interest in taking advantage of committee assistance.

In addition, during the clinical trial, any money received from a commercial sponsor must go through the institution's research funding approval process. Any remuneration has to be reviewed, approved, and issued by the institutional research funding department. As explained by an MOH official, the regulatory solution to researcher's COI has been to disconnect the financial link between the researcher and the sponsor. Instead of refuting the relationship between public institutions and industry, the solution in Israel has been to require transparency and disclosure.⁴⁵⁰

Essentially, rather than restricting the commercial funding of research activities and/or other professional activities, the Israeli regulatory scheme - with the support of the IMA⁴⁵¹ - chose to ensure continued commercial funding but with oversight. There is no doubt that commercial funding is a crucial element for a potentially successful commercialized breakthrough, enhancing innovations. The French regime adopted a similar oversight mechanism to control financial ties between industry and their publicly employed physicians.⁴⁵²

⁴⁴⁷ Interview *supra* note 185.

⁴⁴⁸ *Id.*

⁴⁴⁹ As the representative from the MOH Special Committee explained, once the hospital approves the budget, they have to report their decision to the Special Committee who has 30 days to respond. *Id.*

⁴⁵⁰ Interview with MOH official *supra* note 177.

⁴⁵¹ Within their revised Code of Ethics from 2009, the IMA acknowledges that the strong ties between physicians and the private industry are vital to enable medical progress and advances. The IMA's Code of Ethics *supra* note 123.

⁴⁵² Rodwin discusses the French law enacted in 1993, delegating the responsibilities of overseeing the financial ties between the industry and their physicians to the Order of Physicians. He stated that in France the industry support of

4.2.3 Restricting Private Practice Activities for State Employed Physicians

Lastly, the Civil Service Act restricts state physicians from working in a private sector that conflict with their employment.⁴⁵³ The regulatory regime allows state physicians to spend a certain amount of their time (in return for a 5 percent salary deduction) in various private practices⁴⁵⁴ upon the approval of the Director-General of the MOH or its designee.⁴⁵⁵ In practice, hospital management reviews and approves these requests.⁴⁵⁶ In fact, this provision requires hospitals to internally manage conflict of commitment and interest of their employed physicians. The goal is to prevent hospital employees from engaging in activities that will conflict with their duties as employees.

This regulatory process requiring management approval for any private practice, in fact provides the hospital with access to information regarding their researcher's private engagements. All except one hospital interviewed⁴⁵⁷ indicated that they do not review the information regarding their physicians' private activities in their ethical review for possible COI. To some extent, even though the information is readily available, excluding it from the ethical review for COI makes sense due to the fact that the current regulatory scheme only asks to review COI resulting from the ties with the private biomedical industry and commercial sponsors.

In sum, the current regulatory regime imposes two main procedural processes to address COI concerns arising from public-researchers' ties with commercial sponsors. The first is setting self-reporting disclosure requirements on researchers and institutional review to follow. The second is giving hospitals and in certain circumstances the MOH authority to oversee financial ties prior to the inception of the trial. Additionally, the institutional research fund department

the French physicians' continued medical education, conducting medical research and scientific publications. See Rodwin *supra* note 19 at 12.

⁴⁵³ §42.43(e) of the Civil Service Act (Isr.).

⁴⁵⁴ Physicians authorized to work outside the hospital, will receive a 5 percent deduction from their salary. See *Id.* at §42.43(c).

⁴⁵⁵ *Id.* at §42.43(b).

⁴⁵⁶ According to official from hospital 1: "Per the employment contract, all hospital's employees must obtain the hospital director's approval for working outside. The hospital employee has to notify the director and obtain his/her approval on any employment contract/advising fee based contract with a commercial company." Interview with hospital 1 official, at the official's office at the hospital, Israel (August 20th, 2010).

⁴⁵⁷ Only official from hospital 2 indicated that the head of the R&D department sync the information between employees' working for the industry and his/her research activities/involvement within the hospital. Interview with hospital 2 official *supra* note 436.

oversees any payments issued to researchers throughout the duration of the trial. Public physicians are also restricted in their private engagements outside the hospitals, in the attempt to prevent any conflict with their primary employment duties.

The regulatory framework, however, does not address concerns about other types of researcher COI when it does not directly relate to ties with commercial sponsorship, such as the physicians' own entrepreneurial interests or other nonfinancial-personal interests. Even within the circumstances of financial COI resulting from the relations with the trial sponsor, the regulatory scheme did not specify what affiliations disclosed should be eliminated, or how the hospitals should act to eliminate them. The hospitals are left with the task of defining, assessing, and implementing their own COI policies.

This brief review of the scholarly literature and the regulatory mechanisms has served to highlight a number of issues relating to the definition and use of the concept of individual investigator's COI in the realm of medical research. Subsequent to the regulatory framework overview, the following section is devoted to exploring how those in charge of evaluating and enforcing these regulatory mechanisms are doing so.

4.3 Defining, Assessing and Implications of Researcher COI

The following section focuses on the data obtained from hospital professionals, mainly hospital directors and ethics committee members, who are in charge of defining, assessing and managing and/or eliminating researcher COI. All interviewees explained that, in practice, it is within the Helsinki committee's responsibility to review researcher affiliation disclosures, and to further assess whether affiliations constitute COI.⁴⁵⁸ The head of the ethics committee – Helsinki committee - in one hospital indicated that the Helsinki committee acts as “guardian to the trial participants” making sure that the participants are not harmed.⁴⁵⁹

All interviewees were asked to articulate their experience regarding three main thematic areas: how they define COI at the researcher level; how they assess whether the specific researcher is in

⁴⁵⁸ As discussed in detail in chapter 3, every clinical trials involving human subjects conducted in hospitals, requires a review and approval by the hospital's ethics committee, i.e. the Helsinki committee.

⁴⁵⁹ Interview with hospital 7 official, at the official's office at the hospital, Israel (September 21st, 2010).

COI; and what actions are taken once COI is identified. To control the interviewees' potential bias and to strengthen the internal validity of this research, the goal was to interview several professionals from the same hospital.

Generally, all interviewees expressed a high level of commitment to ensuring implementation of ethical rules and principles in clinical trials involving human subjects. A strong consensus was found among the interviewees regarding the values of ethically conducted research, aligned with international ethical standards, mainly the moral and social values for safeguarding human participants' health and protecting research validity. During the interviews, the interviewees' focused on their important oversight role to make sure that the participants and patients would not be harmed. For example, they described strict overview processes for informed consent and risk and benefit analysis.⁴⁶⁰

In all the hospitals where administrators were interviewed, a process for reviewing researcher affiliation with the trial sponsor was found. At the same time, despite the wide consensus regarding ethical principles, inconsistency was found among the interviewees regarding their definition to what constituted researcher COI and what the necessary consequences of COI were. An interesting correlation was found between the scope of the definition of COI due to sponsor-researcher affiliation, and how the hospitals managed it. In accordance with the thematic approach to the interviews, the following sections are divided into three: COI definition; assessing COI; and consequences of COI.

4.3.1 Hospitals' Definitions of Investigator COI

As part of the regulatory requirement to eliminate COI through mandating affiliation disclosure, hospital officials were asked to describe how they define investigator's COI. The interviewees conveyed diverse opinions on this matter. The diverse views are described in table 4.1 below. In this table, the interviewees' definitions of COI are divided into two perspectives: narrow and broad. The notion of whether the definition is broad or narrow was determined by the nature and

⁴⁶⁰ The Guidelines for Clinical Trials require the institutional ethics committee's analysis that "The foreseeable risks to the trial participant are minimized to the greatest extent possible by the use of appropriate research methods, and where possible, the use of procedures already performed in human subjects or tested in animals". See Guidelines for Clinical Trials *supra* note 35 at § 1.3 e.

scope of the potential secondary interests considered whenever COI is defined. This distinction serves an important role as it provided the framework for how these hospitals assess the circumstances of COI and its consequences.

As the table below shows, the narrow definition encompasses only financial interests resulting from the affiliation between researchers and trial sponsors. As an example of a narrow definition, in Hospital 1, COI circumstances occur when a financial affiliation with the sponsor exceeds the threshold of 10,000 USD. The interviewee explicitly stated that this threshold definition was adopted from the U.S. NIH definition of researcher COI at the time.⁴⁶¹

A broader definition of researcher COI encompasses both financial and non-financial interests. For example, in Hospital 6 the interviewee alleged that the term ‘affiliation’ has no real meaning as both financial and non-financial interests should be part of COI circumstances.⁴⁶²

Table 4.1: Hospitals Definitions to Investigator COI

Type of conflicted interest	Hospital number	Defining Investigator COI
Narrow: Financial affiliation with sponsor	1	Fundamental financial affiliation above 10,000 USD threshold.
		Analysis of the affiliation beyond the financial amount.
	2	Every business-related association excluding fees for participating in conferences.
		Proportionality analysis of the financial affiliation.
	4	Only relevant in non-multi-centered trials.
6 + 7	Proportionality analysis of the financial affiliation – question of how much.	
Broad: Financial and nonfinancial interests.	3	COI is human nature, particularly motivation to publish.
	4	No difference between financial interests and nonfinancial.
	5	Both financial and nonfinancial, particularly motivation to publish.
	6	No real meaning to affiliation, as there is no real difference

⁴⁶¹ Interview with hospital 1 official *supra* note 456.

⁴⁶² Interview with hospital 6 official *supra* note 43.

		between financial and nonfinancial interests.
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As reflected in Table 4.1, inconsistencies were found among the professionals working within the same institution as well. Notable are the differences found in hospitals 6 and 4. In hospital 6, one interviewee described an analysis of the financial affiliation with the sponsor as a matter of amount⁴⁶³; the other representative from that hospital found this analysis to be cumbersome as there is no real difference between financial or nonfinancial interests.⁴⁶⁴ On the face of it, it is difficult to ascertain which of these two approaches in fact reflects hospital 6's COI policy. Especially since the third professional in that hospital, when asked to provide his definition to COI, only asserted that the hospital imposes strict restrictions to ensure ethical compliance.⁴⁶⁵ Arguably, this tension might be resolved by reviewing the interviewees' positions and their involvement in the decision-making in COI circumstances. The interviewee, who belonged to the narrow definition, serves as the head of the R&D department whom the Author was told does not take part in the institution's ethical decisions. The second interviewee, who belongs to the broad definition, serves as the head of the ethics committee in charge of determining COI. Thus, the broad COI definition might carry more weight for hospital 6.

In hospital 4, the first interviewee recognized COI circumstances as being dependent on the size of the trial. He explained that in multi-centered trials, the trial is designed by a big pharmaceutical company with many other institutions involved conducting the trial simultaneously.⁴⁶⁶ In these cases, it would be highly unreasonable for an individual researcher to have an affiliation with the sponsor. This is contrary to small trials where the researcher's role is much more crucial to the sponsor, as the sponsor usually approaches a specific researcher to conduct the trial on their behalf.⁴⁶⁷ On the other hand, another interviewee from hospital 4 indicated that the question of affiliation and trial size is irrelevant, as there is no difference between financial and nonfinancial incentives.⁴⁶⁸ Again, this difference in view may relate to the

⁴⁶³ Interview with hospital 6 official, at the official's office at the hospital, Israel (September 19th, 2010).

⁴⁶⁴ Interview with hospital 6 official *supra* note 43.

⁴⁶⁵ Interview with hospital 6 official, at the official office in the hospital, Israel (September 5th, 2010).

⁴⁶⁶ Interview with hospital 4 official, at the official office at the hospital, Israel (September 7th, 2010).

⁴⁶⁷ In her recent book, Jill Fisher, calls it 'contract physicians' in which mostly in multi-centered trials, these researchers are hired to conduct a predefined research protocols and in fact they do not have any impact on the research design or the interpretation of the end results. See Jill A. Fisher, *Medical Research for Hire: The Political Economy of Pharmaceutical Clinical Trials*, 2 (Gutgers 2009).

⁴⁶⁸ Interview with hospital 4 official *supra* note 466.

interviewee's position and influence in that institution. Debatably, the narrow definition should govern members of the ethics committee. The other opinion was held by a member of the hospital's audit panel, whom as the Author was told was not involved in the preapproval of research or in the hospital evaluation from an ethics standpoint.

There are other nuanced inconsistencies were among interviewees whose hospital's COI definition fell into the narrow category. For example, while in hospital 2 one interviewee recognized that every business relation with the sponsor constitutes COI⁴⁶⁹, another interviewee from that hospital excluded financial relations for the purposes of participating in a conference.⁴⁷⁰ Furthermore, in one way or another, all the interviewees under the narrow definition scope acknowledged some sort of proportionality analysis of the financial relations with the sponsor. However, only the interviewee in hospital 1 stated a strict policy of 10,000 USD as a threshold for proportionality analysis.⁴⁷¹ Others basically explained that this decision would depend on the nature of the financial affiliation and it would be determined on a case by case basis.

4.3.2 Hospitals Assessment of Researcher COI

As opposed to the diverse perspectives on how to define COI in accordance with regulatory provisions, the hospital interviewees were more in consensus as to the kind of resources they use when assessing investigator's COI; the role of the ethics committees; and what their review process for COI should involve. Notably, all the interviewees agreed that it is within the institutional Helsinki committee's authority to review and assess the investigators' COI as part of its job to ensure ethical compliance.

Sources for assessment – formal and informal All the interviewees stated that in order to assess circumstances of COI, the Helsinki committee reviews the investigators' affiliation form submitted by the PI as part of the trial application. Two officials from hospitals 2 and 4 stated that in practice very few investigators actually disclose their affiliation to the sponsor in these forms. One interviewee from hospital 2 estimated that out of 50-60 applications submitted to the

⁴⁶⁹ Interview with hospital 2 official *supra* note 436.

⁴⁷⁰ Interview with another official at hospital 2 *Id.*

⁴⁷¹ Interview *supra* note 456.

Helsinki committee in a month, only 1-2 applications disclosed affiliation to the sponsor. The interviewee believed that this does not reflect the actual number of affiliations with the industry sponsors. She explained that the investigators are probably concerned that once they reveal their affiliation, their research application will be delayed or even declined.⁴⁷² Another interviewee from hospital 4 pointed out that they had 15 cases where investigators did not disclose affiliation with the sponsor and were called by the ethics committee to explain. He explained that in these 15 cases, the committee received a “tip” from other colleagues in which the PI failed to disclose the financial affiliation to the trial sponsor.⁴⁷³ Other hospitals, did not express any concerns as to the accuracy of investigator’s disclosure practices.

Interviewees from all seven hospitals explicitly highlighted that they do not follow up or check the accuracy of the disclosed information as part of their COI assessment. Interviewees were very adamant that hospitals, particularly the ethics committee, rely heavily on the integrity of their physicians-employees, and they never check their information. As one interviewee stated, the system is built on trust.⁴⁷⁴ Another interviewee from the same hospital said that if you cannot trust researchers to accurately disclose information regarding their involvement with sponsors, you cannot really trust them to treat patients.⁴⁷⁵

Notwithstanding the considerable latitude physicians-researchers enjoy, four out of the seven sampled hospitals described an additional “informal” source for reviewing the affiliation disclosure. Hospitals – 2, 3, 4 and 7 – explained that in addition to the “formal resource of disclosure” there is also an informal resource obtained from “whistle blowers”.⁴⁷⁶ They basically agreed that “this is a small country, where everyone knows everyone, and people talk”.⁴⁷⁷ They indicated that such information may not be initially revealed, but “sooner or later” things will come out.⁴⁷⁸

⁴⁷² Interview with hospital 2 official *supra* note 436.

⁴⁷³ Interview with hospital 4 official *supra* note 466.

⁴⁷⁴ Interview with hospital 3 official, at the official’s office at the hospital, Israel (September 2nd, 2010).

⁴⁷⁵ Interview with another hospital 3 official *Id.*

⁴⁷⁶ Interview with hospital 2 official *supra* note 436.

⁴⁷⁷ Interview with hospital 3 official *supra* note 474.

⁴⁷⁸ Interviews with officials from hospitals 2, 3, 4, & 7, conducted at the officials’ offices at the hospitals, Israel (August 31st, September 2nd, September 7th, 14th & 21st, 2010).

These four mentioned hospitals indicated that researchers' failure to disclose information requires some sort of hearing process by the ethics committee or hospital management during which these researchers will be required to explain their failure to disclose the information.⁴⁷⁹ In hospital 2, the interviewee explained that "We trust that researcher unless it is proven otherwise. If later we find out that this person lied, if they publish an article or something disclosing their financial relations with the sponsor, then that person's career is finished."⁴⁸⁰ In hospital 3, the management representative mentioned that "those who lie will not be able to professionally advance" in the institution.⁴⁸¹ Another interviewee from hospital 7 indicated that the Helsinki committee has information about who the "more problematic people in our system" are. He mentioned that the Helsinki committee "treats these problematic people selectively, i.e. checks them much more than others."⁴⁸² This interviewee was reluctant to elaborate why these people were considered "problematic" in his institution.

Role of Helsinki committee – not a research police As part of the interviewees' description of the hospitals' COI review process, all interviewees pointed out that the institutional ethics committee's role does not include an active search for criminals or finding ways to punish researchers. Rather they explained that the Helsinki committee's job is to educate the hospital's employees to ensure ethical compliance. One interviewee in hospital 6 said: "we do not have research police".⁴⁸³ Another interviewee from hospital 2 said, "We are not detectives".⁴⁸⁴ In hospital 7, the head of the Helsinki committee stated that "Beyond the information disclosed by the researcher, we don't check and we don't want to check. I believe that we don't need to search for criminals, but to educate people who didn't know or didn't understand the process."⁴⁸⁵
[Translated from Hebrew]

Assessment of COI resulting from ties with the trial sponsor Following the affiliation disclosure, the hospital officials who adhered to the narrow definition to COI, described a further review regarding the nature and scope of the financial affiliation. In hospital 1, the interviewee

⁴⁷⁹ *Id.*

⁴⁸⁰ Interview *supra* note 436.

⁴⁸¹ Interview *supra* note 474.

⁴⁸² Interview *supra* note 459.

⁴⁸³ Interview *supra* note 463.

⁴⁸⁴ Interview *supra* note 436.

⁴⁸⁵ Interview *supra* note 459.

explained that many of their clinical researchers are indeed senior physicians, and they can have different affiliations which require further review.⁴⁸⁶ Some officials described occasional circumstances where the PIs were called to provide more details regarding their affiliations.⁴⁸⁷ The interviewees could not provide information as to the criteria when PIs were requested to appear before the committee for further clarification. This, as the Author was told, was determined on a case by case basis. With regard to the interviewees who adhered to the broad definition of COI, no further assessment of the affiliation was indicated.

Addressing other types of Investigator's financial COI As mentioned earlier, the regulatory framework does not address other types of COI which are not directly related to the ties with the sponsor. Hence, on the face of it, if the investigator has no affiliation to the trial sponsor, no other information is requested from the trial investigator. As described in the introductory section of this chapter, other types of COI not directly related to the trial sponsor can occur. Such potential COI may include researchers' own entrepreneurial interests (for example holding equity in a startup company), affiliation with a commercial company that manufactures products competing with those being tested in the trial, or even other nonfinancial-personal interests.

Interviewees described process distinctions between commercial trial applications and noncommercial trial applications.⁴⁸⁸ Briefly, only in commercial trials, the industry-sponsor is required to sign a contract with the hospital, pay fees for the hospital and researcher's services for administrating trials and provide a statement from an insurance company covering specific trial related injuries.⁴⁸⁹ In addition, the interviewees explained that this distinction is important for the assessment of COI. They explained that per the regulations, the hospitals review and assess COI relating from ties with the commercial sponsor based on the investigator's disclosure. Whereas in trials initiated by the hospital's physicians, the physician is not required to disclose any additional information for any other possible COI. Some hospitals, as discussed in the next

⁴⁸⁶ Interview *supra* note 456.

⁴⁸⁷ For example officials from hospitals 2, 3, and 6 described a similar ethical review processes. Interviews conducted with these officials at the officials' offices at the hospitals, Israel (August 31st, September 14th & 16th, 2010).

⁴⁸⁸ As the interviewees explained some of the clinical trial applications can be initiated by the hospital employee with no commercial funding.

⁴⁸⁹ The Guidelines for Clinical Trials requires the trial sponsor to provide adequate insurance policy to cover trial related liabilities for the duration of the trial and after. See Guidelines for Clinical Trials *supra* note 35 at § 1.3 (J) & § 9.1.6.

section below, described an additional review and consequences for circumstances where the hospital finds that the employee-PI is requesting to conduct clinical trials with entrepreneurship interests. Three hospitals out of the seven emphasized that these are rare circumstances as only a relatively small number of their physicians-researchers, indeed own stocks or hold equity in commercial companies.

With regard to review and assessment of nonfinancial interests – such as motivation to publish or public recognition – all interviewees were in consensus that these are in fact desired aspirations that need to be promoted at all levels of the institution.

4.3.3 Consequences of Researcher COI

Generally, the relevant literature discusses several possible measures to be enforced by the oversight institution to minimize the risk to research integrity due to financial COI. For example, Shamoo and Resnik maintain three possible strategies: disclosure followed by independent review;⁴⁹⁰ management of COI;⁴⁹¹ or strict prohibition.⁴⁹² One scholar discusses the approach of the University of Pennsylvania for deciding on the extent and level of involvement of the conflicted investigator in the trial. This scholar explains that this policy may exclude a conflicted investigator from serving as the PI, namely prohibiting him or her from developing trial protocols, recruiting participants, obtaining informed consent, and other trial related processes. i.e. such policy is seeking to exclude the conflicted investigator from essentially taking part in critical decisions.⁴⁹³ As mentioned earlier, there is no consensus among institutions worldwide on how to respond to financial COI and what the consequences of being found guilty of financial COI should be to a research professional. Most institutions around the world have adopted some kind of financial COI disclosure policies. For example, The International Committee of Medical Journal Editors (ICMJE) developed a uniform electronic disclosure form⁴⁹⁴, and *JAMA* requires

⁴⁹⁰ They state that the disclosure review should be taken by an party with high level of independence and objectivity, as well as with supervisory role. See Shamoo & Resnik *supra* note 14 at 193-194.

⁴⁹¹ Shamoo & Resnik explain that such COI management is achieved when the oversight body establishes terms and rules aimed to control the secondary interests involved. Some methods to control the conflicting secondary interests may include stricter monitoring and other independent parties to be involved conducting the trial. *Id.*

⁴⁹² Such prohibition can occur when the institution decides to remove the conflicted researcher from the study, or alternatively to renounce the conflicting interests.

⁴⁹³ See Molinoff *supra* note 140 at 287-288.

⁴⁹⁴ The ICMJE's electronic disclosure form is available at their website at http://www.icmje.org/coi_disclosure.pdf, (last visited Sept. 7, 2012).

all authors submitting manuscripts to complete and submit this ICMJE standardized form.⁴⁹⁵ According to Shamoo and Resnik, in the U.S., only a few institutions choose to enforce strict COI prohibition policies.⁴⁹⁶

Similar to the diverse strategies taken by institutions worldwide, hospitals in Israel described different approaches to addressing COI risks and breaches too. Specifically, in circumstances where the investigator disclosed an affiliation to the sponsor, further inconsistency was found among hospitals as to what action should be taken.

Table 4.2 below reflects interview data regarding the hospitals’ various approaches once affiliation was found. This table shows an inverse correlation between the scope of the COI definition and the scope of measures taken by the hospitals, if any, to minimize it. Namely, the more narrow the definition of COI is the more likely that the institutions will enforce more measures to manage it. As this table shows, the interviewees who ascribed to the narrower definition of COI, described additional steps taken by the hospitals in the effort to minimize the risks of bias due to the disclosed financial affiliations. Whereas for the most part, those who ascribed to the broader definition of COI, assert that no additional measures were taken to control or to minimize these conflicted interests.

Table 4.2: Consequences of Researcher COI

Type of conflicted interest	Hospital number	Defining Investigator COI	COI consequences
Narrow: Financial affiliation with sponsor	1	Fundamental financial affiliation above 10,000 USD threshold.	Interested researcher cannot serve as PI or SI.
		Analysis of the affiliation beyond the financial amount.	
	2	Every business-related association excluding fees for participating in conferences.	Affiliated researcher cannot serve as PI but can serve as SI. Excluding rare situations.
		Matter of proportionality of the financial affiliation.	

⁴⁹⁵ On their website, JAMA instruct author to use the ICMJE’s standardized form. See JAMA instructions for authors available at <http://jama.ama-assn.org/offcampus.lib.washington.edu/site/misc/ifora.xhtml>, (last visited Sept. 7, 2012).

⁴⁹⁶ See Shamoo & Resnik *supra* note 14 at 193-194.

	4	Only relevant in non-multi-centered trials.	Only relevant in small non-multi centered trials, excluding consultant-fee affiliations.
	6	Analysis of the financial affiliation – question of how much.	Affiliated researcher might not be involved or PI.
	7	Proportionality analysis of the financial affiliation - depends on the size.	Three options: not conducting the trial; disqualifying the conflicted investigator; or allowing conflicted investigator to serve as PI without limitations. The majority of the cases, the third option.
Broad: Financial and nonfinancial interests.	3	COI is human nature, particularly motivation to publish.	Affiliated researcher can serve as PI. Might require more info in disclosure.
	4	No difference between financial interests and nonfinancial.	Affiliated researcher can serve as PI, as long as the participants are aware.
	5	Both financial and nonfinancial, particularly motivation to publish.	COI is in itself not prohibited. For purpose of publication, investigator might be only registered as a partner and not the main author.
	6	No real meaning to affiliation, as there is no difference between financial and nonfinancial interests.	Affiliated researcher can serve as PI, as there is no real difference between PI and SI.

Narrow scope of COI definition and broad measures The interviewees who ascribed a narrow definition to COI as a result of the affiliation to the trial sponsor, described a spectrum of additional steps taken at their institution in the attempt to eliminate these COI. One strategy frequently raised by the interviewees in that group was to limit the extent and participation of a conflicted investigator. Four out of the five hospitals in this group mentioned that they might exclude an affiliated investigator from serving as PI. Hospital 1 maintained that once the investigator, receives more than 10,000 USD annually from the sponsor, they would be excluded from taking part in the trial.⁴⁹⁷

⁴⁹⁷ Interview *supra* note 456.

Hospital 2 also expressed a strict exclusion policy disallowing affiliated investigators from functioning as PIs, but mentioned that they would allow that investigator to be involved in the trial in a non decision-making role.⁴⁹⁸ Interviewees in hospital 2 however explained that there are infrequent circumstances where this strict exclusion policy would not be enforced. As explained, in rare occasions the hospital might decide to let the affiliated investigator serve as the trial PI. These rare cases occur when compelling circumstances justify such exclusion, i.e. when they find that the affiliated investigator is the only expert who is able to perform the proposed research. As stated by the Interviewee: “There are cases where the PI disclosed the fact that he or she serves as a consultant to a private company. If that company is not sponsoring the specific trial application... we might allow him or her to serve as the PI for the trial. This will require in depth review of the special circumstances following the conclusion that this researcher is the expert in this unique areas, and he or she is the only best person to do that. This is a very rare approval, as in the time I am here there were only about 1-2 cases approved under these circumstances.”⁴⁹⁹ [translated from Hebrew]

Hospitals 6 and 7 allow for the possibility that their hospital would enforce the exclusion policy, but mentioned that doing so is rare. An interviewee from hospital 6 maintained that in some cases the affiliated researcher would not serve as the PI or be involved in the trial, but that each case is evaluated differently.⁵⁰⁰ The interviewee from hospital 7 mentioned three possible strategies: not conducting the trial at all; removing the conflicted investigator from taking part in the trial; or allowing the conflicted investigator to serve as PI without limitations. He explained that in their hospital, in the majority of the cases, the affiliated investigator can indeed serve as the PI with no other limitations.⁵⁰¹

The more lenient approach within the spectrum of measures taken by hospitals was expressed by an interviewee from hospital 4. Per that interviewee, despite acknowledging the mere possibility that some limitation might be imposed on conflicted researchers, he explicitly stated that such a

⁴⁹⁸ Interview *supra* note 436.

⁴⁹⁹ *Id.*

⁵⁰⁰ Interview *supra* note 463.

⁵⁰¹ Interview *supra* note 459.

restriction policy would not be relevant in multi centered trials or cases where the investigator serves as a consultant to the sponsor. This interviewee could not understand why relations of consultant-fees should be excluded nor in what cases the hospital should indeed enforce such an exclusion policy.⁵⁰²

Broad scope of COI definition and narrow measures the interviewees, who could not discern the distinction between financial and non-financial interests for the purpose of defining COI, largely did not see any reason to attempt to eliminate or manage these interests. Arguably, since there is no real way to evaluate or eliminate non-financial COI, why then should hospitals be concerned about evaluating and eliminating financial COI. Notwithstanding the above, all except one hospital (hospitals 4, 5 and 6) expressed that the disclosure requirements should be extended to the trial participants allowing them to decide for themselves.⁵⁰³

An interviewee from hospital 4 stated that once other methodological and ethical elements of the trial (such as informed consent, risk and benefit analysis and processes for recruitment) are met, the question of affiliation to the sponsor in itself is insignificant. This interviewee elaborated that even though the ethics committee does review questions of potential COI, they however have a heavy load of work having to review so much documentation for each trial application. She explained that the ethics committee needs to focus on the “important issues and skip the non-important issues”.⁵⁰⁴

An interviewee from hospital 5 explained that COI in itself is not and should not be prohibited, as the best medical inventions were developed by researchers with clear COI. He gave an example where most of the past invasive cardiology procedures were tested in “someone’s backyard”. However, he did assert that these examples of COI should be disclosed (to the participants too) and be reviewed by the hospital. At the same time, during the interview he mentioned the fact that in some cases, due to the potential risk of biased reporting, the affiliated

⁵⁰² Interview *supra* note 466.

⁵⁰³ Such approach is aligned with the IMA’s code of ethics which requires physician-investigators to disclose any financial interest with industry and any other possible COI to the trial participants. See Chapter D.5 “The Physician and the Commercial companies”, IMA’s Code of Ethics *supra* note 123.

⁵⁰⁴ Interview *supra* note 466.

researcher might only be added as a co-author to the research publication and not as the primary author.⁵⁰⁵

An interviewee from hospital 6 criticized other hospitals' approach excluding an affiliated researcher from serving as a PI but allowing them some involvement in the trial (as secondary investigator). He called such policy "hypocrisy" as there is in fact no real difference between the two roles -- both can be influenced by the conflicted investigator. In his opinion, only disclosing the affiliation to the trial participants constitutes a good response to COI. As he asserted, "COI 'smells bad' when it is concealed."⁵⁰⁶

Lastly, hospital 3 ascertained that an affiliated investigator should and could serve as the trial PI. The interviewee stated that she does not recall any case where they have had to reject a research application or remove the PI from his or her role due to COI.⁵⁰⁷ One interviewee added that their ethics committee might require more information of the affiliation disclosed to understand its nature. As explained, the ethics committee particularly checks whether the participants will benefit from the trial, regardless of the fact that the researcher might have conflicting interests. The hospital committee, as explained, reviews the disclosed affiliation and ensures that there are no other ethical or methodological problems with the proposed research.⁵⁰⁸

Financial COI not resulting from the affiliation with sponsor As discussed earlier other financial COI can occur where the investigator conducting the trial owns stocks in a commercial company or holds equity in a startup company interested in testing their products. As described in the COI assessment section above, in trials initiated by the hospital physician without commercial funding, no additional disclosure is required by the investigator. With no regulatory provision requiring such financial disclosure, some of the hospitals described unsystematic COI review based on informal information. The informal information is obtained from whistle blowers or the fact that hospital staff/ethics committee members know their employee-physicians' private engagements. These officials maintained that it is difficult to hide something like that in small

⁵⁰⁵ Interview with hospital 5 official, at the official's office at the hospital, Israel (September 11th, 2010).

⁵⁰⁶ Interview *supra* note 43.

⁵⁰⁷ Interview *supra* note 474.

⁵⁰⁸ *Id.*

institutions. The inconsistency among the hospitals’ review and response to these types of COI, if at all, is notable. Six out of the seven hospitals did not have a rigorous or systematic strategy to address these types of COI. All except one hospital described somewhat random cases where the ethics committee stepped in to address potential COI.

The abovementioned distinction found between hospitals enforcing a more restrictive policy to eliminate financial COI for affiliated investigators and those who have a more lenient policy toward affiliated investigators, were found to be not applicable for this types of COI issues. Table 4.3 below compares the hospitals’ different approaches to the different types of financial interests. As this table shows, two hospitals – 1 and 2 – were at the two opposite sides of the spectrum presenting completely different approaches in their response to COI. Other hospitals indicated differences in policy.

Table 4.3: Consequences to Different Financial COI – Hospitals Comparison

Hospital	Consequences to sponsor-researcher’s affiliation COI	Consequences of other types of researcher financial COI
1	Interested researcher cannot serve as PI or SI.	No further review or steps are taken.
2	Affiliated researcher cannot serve as PI but can serve as SI. Excluding rare situations.	Rigorous and systematic review of investigator’s private engagement and research activities. Financially interested investigator will not serve as the PI.
3	Affiliated researcher can serve as PI. Might require more info in disclosure.	Not many hospital-researchers have financial interest in studies. Financial invested investigator can serve as PI, as long as everything is done in accordance with the law, with maximum protection to subjects.
4	Only relevant in small non-multi centered trials, excluding consultant affiliations;	Not many hospital-researchers have financial interest in studies. The financial invested investigator may or may not serve as the PI.
	Affiliated researcher can serve as PI, as long as the participants are aware.	No further review or steps are taken.
5	COI is in itself not prohibited. For purpose of publication, investigator might be only registered as a partner and not the main author.	Researchers-inventors are expert on the product, and thus the best person to serve as PI for the benefits of the patients. The participants should be disclosed.

6	Affiliated researcher might not be involved or serve as the PI.	Not many hospital-researchers have financial interest in studies. The financial invested investigator most likely not serves as the PI. However, not sure if this will eliminate the COI. This is a moral decision.
	Affiliated researcher can serve as PI, as there is no real difference between PI and SI.	Disclosing the financial interests to participants.
7	Three options: not conducting the trial; disqualifying the conflicted investigator; or allowing conflicted investigator to serve as PI without limitations. The majority of the cases, the third option.	The majority of the cases, the financial invested investigator will serve as the PI, as long as other regulatory elements are met.

As the table show, despite hospital 1’s strict policy to exclude the affiliated investigator from taking part in the trial, the interviewee explained that their hospital does not conduct any further review, assessment or steps for other types of COI.⁵⁰⁹ Another interviewee from that hospital explained that it would be fairly reasonable to assume that if the investigator was indeed financially invested in the proposed research, then such an investigator would probably want to conduct multi-centered trials in several sites (hospitals) simultaneously to acquire stronger validity for their findings. Per this interviewee, in multi-centered trials “many eyes” are involved as many other physicians-investigators from different sites make the crucial decisions.⁵¹⁰

Hospital 2 was the only hospital that described a rigorous and systematic review in the attempt to minimize the involvement of interested investigators. They maintained that the head of the R&D department review the information regarding the researchers’ request to work for industry, with his or her research activities in the hospital. If they find that such an investigator has a financial interest in the investigated product, they will withdraw him or her from acting as the PI for the trial. They maintained that in order to secure the notion of research validity, such interested investigators should not serve as the PI.⁵¹¹

⁵⁰⁹ Interview *supra* note 456.

⁵¹⁰ Interview with another hospital 1 official, *Id.*

⁵¹¹ Interviews *supra* note 436.

At hospital 3, one of the interviewees acknowledged that, for the most part, financially invested investigators can serve as PIs, as long as the ethics committee finds maximum protection to subjects.⁵¹² They stressed that these cases are pretty rare in their hospital. One interviewee discussed a situation where their employee also owned patent rights to a medical device. The hospital refused to let that researcher bring in his or her own products into the hospital for use with their patients.⁵¹³ It is important to note that this case does not involve COI due to the physician's role as a researcher, but due to his or her role as a clinician.

In hospital 4, the interviewees were divided. While one interviewee believed that financially invested investigators may or may not serve as the PI⁵¹⁴, the other believed that as long as the participants are aware of this investigator's financial incentives, he or she could serve as the PI.⁵¹⁵ The first interviewee pointed out that only a relatively small number of their researchers are working in the industry or owns rights in medical product companies. He gave an example where the ethics committee approved the PI who also owned a private lab to conduct the trial. He mentioned that everybody knew that this PI made a lot of money as a result of the trial. He added that as a matter of policy, the hospital needs to be careful about these cases. Another interviewee could not see any problem with financially interested investigators serving as the PI, as long as the participants were aware of that interest. she stressed the fact that it is in their hospital's interest to promote scientific progress, and to provide the people with the best medications.

Hospital 5 emphasized the fact that researchers-inventors (holding IP rights to the tested product) are in most cases the best people to conduct the trial as they are the experts on their inventions. The interviewee acknowledged that it is in the best interests of patients, that such an expert conducts the trial and not someone with less background or relevant expertise. This is particularly true in surgical procedure trials. The interviewee believed that participants should disclose all financial interests. He further stressed that it is in the hospital's interest to promote innovations by their employees.⁵¹⁶

⁵¹² Interview *supra* note 474.

⁵¹³ *Id.*

⁵¹⁴ Interview *supra* note 466.

⁵¹⁵ *Id.*

⁵¹⁶ Interview *supra* note 505.

Similar to hospital 4, interviewees from hospital 6 were divided on the issue. While one interviewee recognized that in most cases the financially invested investigator will not serve as the PI⁵¹⁷, the other interviewee only recognized the need to disclose the information to the participants.⁵¹⁸ The first interviewee doubted whether removing the interested investigator from their role as the PI would indeed eliminate the COI. He raised a question whether other physicians in the interested investigator's department might be influenced or directed by that person. This interviewee, however, provided two exceptions to the PI exclusion policy. In cases where the trial is only in its early stage, the chances that this product will indeed reach the market are very low. In these early stages, it is still hard to understand the financial stakes as these are not yet crystallized. Thus, at that early stage, he believed that there should not be any problem with such an investigator serving as the PI. Another exception was mentioned, similar to hospital 5, where the interested PI is the only expert to conduct the trial. The interviewee stated that in these cases, it is in the best interests of patients that such investigators serve as PI. The second interviewee, similar to the interviewee in hospital 4, stated that as long as the financial interests are disclosed to the participants, no other restrictions should apply.

Lastly, hospital 7 also did not see a reason why in the majority of the cases, the financially invested investigator could not serve as the PI, as long as other regulatory elements – informed consent, risks and benefits analysis etc - were met.⁵¹⁹

4.4 Discussion and Analysis of Interview Findings

The abovementioned review of the interviews data and the regulatory mechanisms have served to underline a number of issues relating to the practical use of the COI concept in the biomedical research involving human subjects at the individual researcher level. All hospital officials interviewed expressed, in some way or another, a strong position in which their public-physicians essentially desire to act in a legal and ethical manner. Rather than creating stringent rules and clear standards, hospitals default to government COI principles for guidance as the acting institutional oversight parties. Based on the regulatory provision and the interview data,

⁵¹⁷ Interview *supra* note 43.

⁵¹⁸ Interview *supra* note 463.

⁵¹⁹ Interview *supra* note 459.

the next sections will discuss issues relating to the implementation of the current governance framework in terms of roles, standards and responsibilities.

4.4.1 Ambiguous COI Provision – Incoherent COI Policies among Hospitals

The regulatory COI principle requires that medical institutions work toward eliminating COI resulting from employee-investigator association with the trial sponsor. The standards for making such COI judgments are unspecified. Hospital ethics committees are left to fill in these standard gaps. As the interviews data suggest, inconsistencies were found in the interpretation and implementation of the COI principle by the various medical institutions. While some hospitals were willing to recognize the financial affiliation with the sponsor as a COI risk, others were not. In the latter group of hospital professionals, for the most part, the regulatory COI principle is thus meaningless.

Can a general and unspecified regulatory COI principle enable good research governance practices? Can the variations found among hospitals be considered good governance practices? Representatives within the MOH have differing opinions. Per one MOH official, the answer is yes. This official believes that having such a broad provision leaves the hospitals with considerable latitude in their decision-making authorities. In her opinion, providing too much detail might indeed resolve some of the issues, but it could also add other complications. It is extremely hard to be able to clearly and accurately draw the line where COI begins or ends. She believes that it should be up to the ethics committees to decide.⁵²⁰

On the other hand, the Director-General of the MOH believes that the regulatory approach has to be paternalistic and leave very little room for discretion. He stated that as part of the MOH's responsibility to ensure the public's health, it should thus provide a clear framework for hospitals to work within. He states that there should be clear rules about when affiliation constitutes prohibited COI, leaving little discretion to the hospitals to interpret. He agreed that the regulatory provisions cannot always anticipate all possible gray areas, but it is up to the regulations to cover

⁵²⁰ Interview *supra* note 177.

as much of these gray areas as possible. He believes that the MOH needs to establish clear roles and policy regarding researcher's COI.⁵²¹

In the U.S. the literature frames the need for clear rules and standards for COI policies from a governance perspective on the element of transparency. The U.S. IOM report offers criteria necessary to evaluate actual operation of current COI policies. In accordance with the IOM report, transparency is a crucial feature necessary when administrating COI policies.⁵²² The IOM report stipulates that “Transparent policies are readily available in clear and simple language, together with explanation and essential information about their application. They are also available not only to those who are subject to them... but also to other stakeholders, including the public. Transparency is essential in determining whether conflict of interest policies are reasonable and if they are implemented fairly.”⁵²³

Good public governance relies on well-defined standards, norms and processes as well as solid public arrangements to implement them.⁵²⁴ Transparently identifying these aspects and reviewing their relations is the foundation for a thorough and consistent governance framework for the biomedical research arena. Apparently, the current Israeli regime, in reflecting upon its stand on essential COI standards and processes, leaves the hospitals and the public with some fundamental unresolved questions.

Not only does the lack of clarity around COI fail to reflect the regulatory stand on researcher COI to the hospitals, but it might also introduce a biased interpretation. Existing literature shows that at least in financial COI situations, the more broad and ambiguous the COI policy is, the more likely the financial self interest will impact investigators' judgment. As discussed by Yuval Feldman's, a well known Israeli scholar, studies show that the more we deal with situations where the self-interest to breach the COI provision is higher, wording it broadly will increase the

⁵²¹ Interview with the Director-General of the MOH, at his office in Jerusalem, Israel (September 20th, 2010).

⁵²² See the IOM report *supra* note 32 at 58.

⁵²³ *Id.*

⁵²⁴ Marie Hirtle, The Governance of Research Involving Human Participants in Canada, 11 Health L.J. 137 (2003).

chances of its breach.⁵²⁵ Thus, Feldman argues that the literature supports adopting clear COI legislation with little room for interpretation identifying all potential conflicted situations.⁵²⁶

4.4.2 The Self-Reporting Disclosure and the Informal Sources

For the purposes of clinical trial applications, individual researchers in Israel are by and large self-reporting the scope of their affiliation with trial sponsors. Generally, the scholarly material worldwide supports the disclosure strategy as useful to address COI since it sets the conflicts out in the open allowing others to assess them.⁵²⁷ Furthermore, disclosure is seen as promoting trust as people who tend to be more suspicious and untrusting when they discover previously hidden conflicts.⁵²⁸

However, some compelling research findings have brought this self-reporting mechanism into question. A 2009 U.S. study assessed the accuracy of investigator's COI disclosures of payments received from manufacturers of orthopedic devices.⁵²⁹ This study showed a high rate of nondisclosure of payments by the scientists who either presented, or served as a committee members or board members at the 2008 annual meeting of the American Academy of Orthopedic Surgeons. It found that a total of 20.7 percent of directly related payments received, and 50 percent of indirectly related payments received were not disclosed. It also found that the undisclosed payments were substantial: 43 undisclosed directly related payments totaled more than 4 million USD, while the undisclosed indirectly related payments totaled more than 7 million USD.⁵³⁰ The U.S. IOM report also discusses these emerging studies showing concerning practices of researchers failing to disclose substantial payments from drug companies, as required by their employer, the government agencies or medical journals.⁵³¹

⁵²⁵ See Feldman *supra* note 76 at 109.

⁵²⁶ *Id.*

⁵²⁷ Shamoo & Resnik *supra* note 14 at 193-194.

⁵²⁸ *Id.*

⁵²⁹ In that study, the authors compared the payments reports to physicians published by five manufacturers of hip and knee prostheses in 2007, with information of payments disclosed by scientists who presented, served as a committee member or board member at the 2008 annual meeting of the American Academy of Orthopedic Surgeons. See Okike K et al. *supra* note 13.

⁵³⁰ *Id.*

⁵³¹ See IOM report *supra* note 32 at 3.

Currently, there are no empirical data analyzing the frequency, extent and/or accuracy of physicians' self-reporting in Israel. Cases of nondisclosure rarely receive any public attention as hospitals are not in the practice of publicizing violations of disclosure. Two interviewees from hospitals 2 and 4, however, suggested that their investigators failed to disclose such information.⁵³² Based on the interviews conducted with hospital officials, particularly members of ethics committees, all the interviewees maintained that their institutions are not checking the accuracy of the disclosed information. They noted that they do not consider themselves research police. All hospital interviewees agreed that the Helsinki committee's role is to educate the institution's employees to ensure regulatory and ethical compliance. The officials at the MOH explained that the regulatory regime does not include any noncompliance provisions for the oversight bodies. The MOH officials also maintained that the MOH does not have "a black list of doctors who have committed horrible acts".⁵³³

In Israel, the penal code provides the main mechanism for addressing COI under the current legal regime. Punishing those who abuse their research responsibilities is governed under the penal code. Thus, despite the proactive attempt to address COI by virtue of disclosure mechanisms, there is still a high level of reactive judicial scrutiny through criminal prosecutions for COI and research misconduct. As specified by an interviewee from hospital 2, in Israel, most cases of public physician and researcher misconduct are dealt with through criminal law especially through the use of the breach of trust offense. He explained that the breach of trust offense is interpreted by the courts very broadly, and is used mainly in order to fight bribery in the public sector.⁵³⁴ Other mechanism to address violation of COI by physicians is disciplinary proceedings instigated by the MOH.⁵³⁵ As explained by one of the interviewee, a member of this MOH disciplinary committee⁵³⁶, any formal complaint against doctors has to be approved by the deputy Director General of the MOH while the doctor is legally represented.⁵³⁷ The disciplinary committee has the authority to recommend several actions including, remarks in the doctor's

⁵³² Interviews *supra* notes 436 & 466.

⁵³³ Interview with MOH officials *supra* note 313.

⁵³⁴ Interview *supra* note 436.

⁵³⁵ The MOH is authorized to instigate disciplinary proceedings against doctors, inter alia, in cases where a doctor acted in inappropriate manner. See the Medical Practitioners Ordinance [Amendment] Law 5736-1976 at §41-47.

⁵³⁶ In order to protect the anonymity of the interviewee participating in this study, the Author decided not to include any information about the interviewee mentioned in this section.

⁵³⁷ *Id.* at §44.

records, reprimand, a severe reprimand or license temporary debarment from a month period to lifetime.⁵³⁸ Per the interviewee, this is a very cumbersome legal process when often times the formal complaint is submitted years after the incident, while the doctor keeps practicing in the meantime. In his view, such a mechanism is not an effective tool to deter wrong doing. A better mechanism that provides tools for actions against ethical violations in real time would be a significant improvement.⁵³⁹

Monitoring and enforcing noncompliance for COI disclosure was discussed by the Association of American Medical Colleges (AAMC) task force on researcher financial COI in clinical research in 2001.⁵⁴⁰ In their policy guidelines, the AAMC recommended that financial COI policies should be comprehensive and include specific sanctions for noncompliance (including nondisclosure), along with constant monitoring by the institution's oversight bodies.⁵⁴¹ They clarified that any COI policy should consist of well defined possible sanctions for noncompliance, including dismissal.⁵⁴² The literature in the U.S. acknowledges the possible actions taken by the oversight bodies when COI information is disclosed to them⁵⁴³, but insists on the mandatory and comprehensive disclosure requirement.⁵⁴⁴

The interviewed hospital officials in Israel, however, have expressed a reluctance to be detectives in their oversight of investigator disclosure. They indicated that such monitoring responsibilities are unnecessary in medical institutions in Israel due to the constant flow of 'informal' information. Interviewees explained that even though research misconduct due to concealed affiliation with the sponsor is possible, Israel is a small country and things tend to be discovered eventually.⁵⁴⁵ Most interviewees indicated that informal sources of information are

⁵³⁸ *Id.* at §41.

⁵³⁹ In order to protect the anonymity of the interviewee participating in this study, the Author decided not to include any information about the interviewee mentioned in this section.

⁵⁴⁰ Association of American Medical Colleges & AAMC Task Force on Financial COI in Clinical Research, *Protecting Subjects, Preserving Trust, Promoting Progress: Policy & Guidelines for the Oversight of Individual Financial Interests in Human Subjects' Research*, (Washington D.C. 2001).

⁵⁴¹ *Id.*

⁵⁴² *Id.* at §B 15.

⁵⁴³ Johnston argues that the decision on how to deal with the disclosed information should vary depending on the nature and materiality of the COI. See Johnston *supra* note 365 at 25.

⁵⁴⁴ *Id.*

⁵⁴⁵ Such as interview *supra* note 474.

available due to the fact that Israeli hospitals are relatively small and “everybody knows everybody”.⁵⁴⁶

Apart from “informal” resources, some solutions to the potential risks of undisclosed COI by researchers can be found in the legislative disclosure and reporting act.⁵⁴⁷ This statutory provision imposes reporting requirements of any monetary donation or donation of worth made by drug and medical device companies operating in Israel to a variety of recipients, including physicians-researchers. Disclosures are imposed upon both the donor and the recipient⁵⁴⁸, to be forwarded and published by the MOH. Such reporting mechanisms will no doubt increase transparency, allowing both the public and the MOH access to essential information relating to potential COI. Since this reporting applies to both researchers and institutions, it will also enable scientists, hospitals, policymakers and even the public to identify the prevalence of COI at the individual level. However, the willingness, the scope and effects of such wide reporting requirement is yet to be seen.

4.4.3 Can Disclosure Alone Be Sufficient to Safeguard the Primary Goals of Research?

As discussed earlier, the regulatory COI mechanism demands researchers to disclose their affiliation to the trial sponsor, in order to enable institutions to assess whether these have developed into prohibited COI. Several hospital professionals interviewed opined that the disclosure in itself is a sufficient tool to address the risks of these types of COI, as long as affiliations were disclosed to the trial participants in the informed consent process.

Indeed while disclosure is the strategy most commonly imposed for dealing with financial COI worldwide, the literature supports that disclosure itself is not sufficient to safeguard professional integrity or to maintain the public trust.⁵⁴⁹ Thompson argues that disclosure mechanisms can cause ‘deficiency of disclosure’. Such deficiency entails the risk that those who review the disclosed information, particularly trial participants, may not know how to interpret it, or may

⁵⁴⁶ See interview *supra* note 435.

⁵⁴⁷ See *supra* note 188.

⁵⁴⁸ With regard to physicians, the threshold for disclosure is annual donations of more than 2,500 NIS.

⁵⁴⁹ The IOM report *supra* note 32 at 8.

not have other alternative courses of action.⁵⁵⁰ He warns that financial COI information may only foster anxiety among the trial participants, causing more suspicion which ultimately undermines their trust.⁵⁵¹ In view of this deficiency of disclosure, IOM report warns that merely disclosing the information without taking additional steps to eliminate or manage COI, will probably continue to pose risks to objective judgment and weaken the public trust.⁵⁵²

As discussed in Chapter 2, the former Chief Judge of the Israeli Supreme Court, Haharon Barak, seems to agree that disclosure in itself will not neutralize the prohibited COI. Barak asserts that disclosure is irrelevant, since the pragmatic and normative goals of the COI doctrine are not met by merely disclosing COI.⁵⁵³ Support for such an approach can also be found in the old teaching of the Jewish Law.⁵⁵⁴

4.4.4 The Regulatory COI Principle Addresses Certain Types of COI

Despite the proactive attempt to address COI through disclosure mechanisms, these mechanisms in Israel in fact are only partial. Not only does the regulatory provision for COI assessment lack important definitions and standards, it also addresses only certain types of COI: The regulatory framework only addresses potential COI resulting from sponsor-investigator affiliations (whether financial or personal associations). This rule apparently focuses entirely on the attempt to prevent bias in research in light of the financial ties between industry and hospital-employed researchers. Other areas of COI concerns discussed in the literature, such as benefits to researchers' own entrepreneurial interests, are not officially addressed.

On the face of it, one can argue that other types of financial COI were not recognized by the Israeli regulatory regime as potential risks to research validity and research participants' health. This was the perception of the hospital 1 interviewee who argued that per the regulatory silence on the matter, the ethics committee does not implement any steps regarding these other types of

⁵⁵⁰ Thompson *supra* note 34 at 295-297. Also see George Lowenstein, Sunita Sah & Daylian M. Cain, The Unintended Consequences of Conflict of Interest Disclosure, JAMA 307(7) 669 (2012).

⁵⁵¹ *Id.*

⁵⁵² The IOM report *supra* note 32 at 8.

⁵⁵³ See Barak *supra* note 75 at 43.

⁵⁵⁴ See Hacohen *supra* note 64 at 175.

COI.⁵⁵⁵ Some of the other hospital interviewees, however, seemed to disagree. For the most part, five out of the seven maintained some sort of review and took measures when they found investigators motivated by personal financial incentives. Hospital 2 went as far as to exclude such investigators from any decision-making role.⁵⁵⁶ Others were less willing to implement such a strict policy, and undertook some form of additional evaluation whether or not such interested investigators could be involved.

Such inconsistency is problematic. It may expose investigators to confusing practices particularly when investigators choose to transfer from one hospital to another. It also provides confusing messages to the public who are left to ponder why certain types of financial incentives are deemed risky and others are not. These concerns for other types of financial COI now supported by emerging worldwide empirical data require further review and assessment by both the institutions and the Israeli regulator.

4.4.5 State Investigator Private Practice Information Is Readily Accessible

Israeli law limits physicians working for the state from working in the private sector if such work conflicts with their employment requirements. In order to be able to work outside the hospital, all public physicians are required to apply and receive the hospital's management approval in advance. This review and approval mechanism provides the hospital, at least state owned hospitals, with access to essential information regarding their employee-researcher's private engagements. Thus, even without a formal regulatory disclosure of such activities for the purposes of conducting clinical trials, the hospital management already has that information in their records.

In practice all but one hospital indicated that they do not synchronize the information regarding their physicians' private activities in their ethical review for possible COI. Only one hospital – hospital 2 – indicated that their R&D department indeed synchronizes the information from their researchers' private practices and their research activities.⁵⁵⁷ To some extent, even though the information is readily available to the ethics committee, excluding it from the ethical review for

⁵⁵⁵ Interview *supra* note 456.

⁵⁵⁶ Interview *supra* note 436.

⁵⁵⁷ Interview *supra* note 436.

COI might be reasonable since the current regulations do not require such review. Having said that, with today's entrepreneurial research environment, new conflicts are generated for the stakeholders involved which raises more concerns for bias in research. These concerns not only necessitate reevaluation of the current policies for the extent of disclosure, but also reevaluation as to whether the overseeing bodies should utilize multiple sources of information for COI assessment.

4.4.6 Oversight By the MOH Special Committee – Mandatory Only in State Owned and Clalit Owned Hospitals

Lastly, part of the requirement to regulate ties between sponsors and public researchers is incorporated within the Director-General of the MOH guidelines. This mechanism authorizes the MOH Special Committee to review and approve trial sponsorship contract and budget plans.⁵⁵⁸ This MOH Special Committee is also authorized to review and approve physicians' travel and conferences expenses as well as physicians' continued medical education proposals. Notably, this MOH Special Committee, however, is only authorized to review research budget plans or other expenses issued by government owned institutions and those owned by the Clalit Health Fund. For these institutions it is a mandatory review; for other public medical institutions it is voluntary. According the MOH Special Committee interviewee, such special review mechanisms were also offered to other research institutions in Israel, but they showed no interest in participating in them.⁵⁵⁹ Having a government's preapproval review and assessment of trial sponsorship apply to certain public hospitals and not to other hospitals is problematic.

This is an anomaly, as it is not clear why some institutions are required to undergo such mandatory review and approval processes to safeguard from COI, and others are not. The interviewee from the MOH's Special Committee expressed his view that such review and assessment should be mandatory for all medical institutions conducting commercial-sponsored-trials.⁵⁶⁰ Such unexplained distinctions among the public hospitals, may create a sense of an institutional hierarchy. Arguably, per this distinction some institutions are considered by the

⁵⁵⁸ See the Procedure for Reviewing Contractual Agreements *supra* note 301. This special committee is a joint committee appointed by the Director-General of the MOH and the Clalit Sick Fund.

⁵⁵⁹ Interview *supra* note 185.

⁵⁶⁰ *Id.*

government as capable of ensuring ethical compliance without government oversight, while others are not. If the MOH found it necessary to include such review and approval mechanisms in the attempt to regulate the relations between public physicians and commercial sponsors, this procedure should be assigned to all public institutions who participate in human subject medical research.

4.5 Conclusion

Individual researchers conducting clinical trials on human participants, have various responsibilities to produce a valid scientific study and to ensure participants' safety. These primary goals were interpreted broadly by the regulatory framework and the judicial branch, extending the boundaries of responsibility beyond the trial period and beyond the scope of the particular participants to the public as a whole. With trial researchers enjoying significant control over critical phases of research, and the entrepreneurial nature of the medical research, concerns for COI are constantly emerging. The main COI concern is whether personal conflicting interests can undermine investigator's primary responsibilities.

Worldwide studies have suggested that the increasing number of collaborations with industry has in fact inappropriately impacted research findings and publications. Other studies suggested more investigators are actively pursuing profit and commercial avenues alongside their research work. The concerns for financial COI have produced a number of regulatory safeguards in Israel, including affiliation disclosure requirements, institutional and governmental review processes, and approval processes for state physicians private practices. Rather than creating stringent rules and clear standards, hospitals default to government COI principles for guidance as the acting institutional oversight parties.

A strong consensus was found among the hospital interviewees regarding the values of ethically conducted research aligned with international ethics standards. All held to moral and social values for safeguarding human participants' health and protecting research validity. However, despite wide consensus regarding ethical principles, inconsistency was found among the hospitals in practice, specifically what constitutes COI at the researcher level, and what the necessary consequences of such COI are. An inverse correlation was found between the scope of the definition of COI due to sponsor-researcher affiliation, and how the hospitals reportedly

managed it: the narrower the definition of COI adopted by the hospital reviewers, the more specific were the measures taken to eliminate or manage COI.

The foregoing review of the implementation in practice of approaches to investigator COI in Israel raises a number of research governance practices issues. Issues discussed in this chapter were based on information derived from government guidance and numerous interviews with hospital representatives and government oversight officials. The following are the main conclusions:

- The broad and unspecified COI regulatory provision fails to reflect the Israeli scheme's stand on researcher COI;
- Hospitals reluctance to oversee disclosure compliance and the informal source of information for COI assessment;
- The "deficiency of disclosure" particularly for trial participants;
- The inconsistency of regulatory attempt to address COI by virtue of disclosure mechanisms;
- The limited sources for financial COI assessment implemented by the hospitals; and
- The regulatory anomaly of imposing COI review and approval processes only on certain medical institutions.

CHAPTER 5: Conflict of Interest – Institutional Ethics Committees and Government Advisors

This thesis examines the governance, operations and practices of Israel's biomedical scheme safeguarding against the risks associated with COI in biomedical research. In six sections, this chapter attempts to theorize the conceptual and practical nature, extent and consequences of COI ascribed to institutional ethics committees and government advisory committees who are assigned to ensure regulatory and ethical compliance in clinical trials in Israel. Similar to Chapter 4, this chapter is designed to evaluate whether the current regulatory framework and practices are adequately responding to the COI of the stakeholders responsible for ethical review in clinical research in Israel. It incorporates two levels of analysis: conceptual and practical. The conceptual analysis, discussed in sections 5.1 and 5.2, explores the Israeli regulatory model directed at the protection of the primary goals of clinical research by virtue of independent review and oversight mechanisms. These regulatory review and oversight responsibilities are mainly bestowed upon the institutional Helsinki Committee and/or the officials at the MOH. It demonstrates how the entrepreneurial nature of biomedical research, and the associations between the research reviewers and sponsors, creates several COI issues which challenge the core design of safeguards. The main concern centers on whether the increasing commercial sponsorship and growing financial incentives for reviewers and/or their institutions may have or be perceived to have impact on the reviewers' impartiality.

The practical analysis, discussed in sections 5.3 and 5.4, describes how the Israeli regulatory framework distinguishes between the different actors involved in the research review process. While the various government advisory committees are governed by specific COI disclosure and management requirements, the institutional ethics reviewers are left to develop their own internal policies on COI related to their members. It then proceeds to discuss the information obtained from the interviews conducted with hospital representatives, members of the government advisory committee (the National Ethics Committee) and government officials to understand the processes and policies responding to reviewers COI. Overall, the interview data supports a conflict avoidance policy, where the reviewer-PI recuses him or herself from the discussion and decision-making process. Nevertheless, variations were found between institutional reviewers

and government advisor reviewers with regard to the scope and definition of COI when other possible interests are involved.

The critique of this chapter, discussed in section 5.5, centers on the practical analysis of the implementation approaches to research reviewers' level in Israel. The following are among the critiques advanced in this chapter: the "Shared Pool Dilemma" raising tension between impartiality and competence, which increases the challenges for recruiting members to government advisory committees; the "disclosure deficiency" problem makes it difficult to interpret disclosed COI information under the current provisions; and the lack of regulatory COI provision for the institutional actors, creates inconsistencies in interpretation and implementation, as well as narrow application of the hospital internal COI policies. The last section 5.6 discusses, summarizes, and concludes the main findings.

5.1 Review of Research Protocols and Oversight – Safeguarding Ethical Conduct

The next section describes Israel's independent review and oversight model, shifting from a centralized state-run review paradigm to a decentralized state-institutional model. Based on this state-institutional model, safeguarding the ethical conduct of medical research is mainly assumed by the institutional Helsinki Committee and/or the MOH. Moreover, as part of the ethical or scientific evaluation, the MOH is assisted by various professional committees and/or experts. The section to follow briefly describes the characteristics and regulatory responsibilities of four key stakeholders: the institutional Helsinki committees; the government advisory committees; government central committees; and ad hoc experts.

5.1.1 Background – State-Run Paradigm with Limited Institutional Review

Research institutions, ethics committees and government agencies have the responsibility of ensuring that research conducted within their bailiwick conforms to standards of scientific integrity and adequately protects human participants (hereinafter: the primary goals). In order to safeguard these primary goals, many Western countries⁵⁶¹, including Israel, promulgate requirements aimed at protecting the general ethical principles governing biomedical research

⁵⁶¹ Over time many of the Western-style countries – including the U.S., the EU, Australia and Japan - developed a consensus standards and procedural requirements for clinical trials involving human participants. See Baruch Brody, *The Ethics of Biomedical Research: An International Perspective*, 35-36 (Oxford 1998).

involving human subjects. The standardized requirements developed by various nations include the following: informed and voluntarily consent from participants; positive risk-benefit ratio; equitable selection of subjects; privacy protection; and preapproval and oversight by an independent committee.⁵⁶²

The independent preapproval and oversight concept was originally developed to counterbalance investigators' conflicting obligations to both pursue scientific inquiry and safeguard the health of their patients and participants.⁵⁶³ Safeguarding the rights of clinical trial participants was no longer left only in the hands of the scientific community.⁵⁶⁴ As the U.S. Tuskegee Syphilis Study Ad Hoc Advisory Panel of 1973 concluded regarding, inter alia, the Tuskegee Syphilis Study⁵⁶⁵: "Society can no longer afford to leave the balancing of individual rights against scientific progress to the scientific community alone."⁵⁶⁶

Indeed many Western countries have established ethics committees to fulfill the requirement for objective independent review. These ethics committees are charged with reviewing research protocols to analyze potential ethics violations, and acting as "gatekeepers"⁵⁶⁷ for trial participants through oversight. Primarily these ethics committees are responsible for protecting the safety and well-being of research subjects. Some scholars contend that such review mechanisms serve yet a bigger role. They argue that research review mechanisms reflect the local society's obligation to its people to maintain methodically reliable and ethically sound

⁵⁶² *Id.* at 36-37.

⁵⁶³ The U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research addressed this research and practice inherent conflict in its 1978 report. See *supra* note 28. In fact, this profound conflict was the primary reason why U.S. federal agencies insisted on having independent ethical evaluations by ethics committees. See Lemmens *supra* note 29 at 747-757.

⁵⁶⁴ The Declaration of Helsinki by the World Medical Association, for example, acknowledged the conflict between the "importance of the research objective and the inherent risk and burdens to the research subjects". Thus, the Declaration requires investigators to conduct a thorough risk and benefit analysis along with a detailed informed consent processes. See the Declaration of Helsinki *supra* note 33.

⁵⁶⁵ The Tuskegee syphilis study aimed to explore the natural progression of the syphilis disease. During the course of forty years, investigators observed around four hundred African-American men infected with the disease, and two hundred other African-American men disease free as the control group. These subjects were not informed of the nature of their disease nor the fact that this study had no therapeutic benefits and ultimately harmed them as treatment was withheld. As a result, at least 28 participants had died and approximately a hundred suffered from untreated syphilis complications. For more information about Tuskegee's study, see The Human Radiation Experiments, the final report of the Advisory Committee on Human Radiation Experiments, 102-104 (Oxford 1996).

⁵⁶⁶ See the Tuskegee Syphilis Study Ad Hoc Report *supra* note 1.

⁵⁶⁷ See Schatz *supra* note 229.

research, as well as hold true to its commitment to strengthen the public trust in its research systems.⁵⁶⁸

Although many countries require approval and oversight mechanisms by ethics committees, and there is consensus on general ethical frameworks, the procedural requirements and the responsibilities of these ethics committees vary among countries.⁵⁶⁹ Until 1980, the Israeli oversight of biomedical research was a state run review model where all research applications were subject to approval by the Pharmaceutical Administration at the MOH.⁵⁷⁰ As discussed in Chapter 2, before 1980 no formal procedures for the application, review, or approval of clinical trials existed. In view of the growing number of trial applications and the necessity to obtain regulatory approval in a timely manner, the Director General of the MOH enacted the Public Health Regulations.⁵⁷¹ The Public Health Regulations enabled, for the first time, the decentralization of certain review and approval authorities within medical institutions. The Public Health Regulations - and the Guidelines for Clinical Trials issued later by the MOH Pharmaceutical Administration⁵⁷² - specify different responsibilities for ensuring regulatory and ethical compliance in research studies depending on the nature of the research, and whether vulnerable participants are used. These specifications and the approval process are discussed in detail in Chapter 3.

Briefly, as discussed in Chapter 3 section 3.5, the regulatory scheme differentiates between “*special trial*” and “*non-special trial*” applications⁵⁷³, while the institutions have the authority to review and approve only “special trial” applications, all other trials are considered to be “Non Special Trials” and require the approval of the MOH.⁵⁷⁴ The decision about whether an

⁵⁶⁸ For examples see Kathleen Cranley Glass, Questions & Challenges in the Governance of Research Involving Humans: A Canadian Perspective in in Law & Ethics in Biomedical Research: Regulations, Conflict of Interest, and Liability 38 (Trudo Lemmens & D. Waring ed. Uni. of Toronto 2006).

⁵⁶⁹ For the apparent differences in terms of role, authority and other procedural requirements with respect to the ethics committees among various countries, see Bowen *supra* note 340 at 552-559.

⁵⁷⁰ See Bilig *supra* note 136.

⁵⁷¹ See Public Health Regulations *supra* note 138.

⁵⁷² The Guidelines for Clinical Trials *supra* note 35.

⁵⁷³ As discussed in details in chapter 3, the regulations defines “*Special Trial*” as one that aims to test a medical product for use in Israel that was already accepted by a “*recognized country*”, or for purposes not specified on that product’s label. See *Id.* at §6.

⁵⁷⁴ See *Id.* at §1.

application calls for a Special or Non Special Trial is made by the specific hospital's ethics committee – in Israel they are called the Helsinki Committees.

5.1.2 The Stakeholders Responsible for Ethical Review and Oversight - Overview

Generally, the Israeli biomedical regime acknowledges that ethically conducted research entails an essential safeguard of moral and social values, such as human health, safety and scientifically valid research.⁵⁷⁵ The responsibility for the evaluation and oversight of human subject research is imposed on the following main stakeholders: the participating medical institution's governing Helsinki Committee (Israel's medical institution ethics board)⁵⁷⁶, its Director, and/or the Director General of the MOH or its designees.⁵⁷⁷ In practice, the Director General of the MOH has delegated this authority to the Pharmaceutical Administration at the MOH.

National Ethics Committees To assist the MOH with its review and approval mission, the statutory government advisory committee was established - the National Ethics Committee ("National Committee") - to obtain expert input on scientific, technical, and ethical issues.⁵⁷⁸ A mandatory review and approval by this National Committee is imposed when trial applications relate to genetic testing, in vitro fertilization or other circumstances that the MOH sees as requiring further input.⁵⁷⁹

An additional government advisory committee was convened by the MOH to advise it on issues related to gene therapy research applications. As explained by the MOH officials interviewed, with the field of emerging gene therapy, further discussion and analysis on its scientific and ethical merit was required.⁵⁸⁰

Central Committees In addition to these two special government advisory committees, the Pharmaceutical Administration of the MOH also uses various Central Committees for further recommendations regarding trial applications not covered under the aforementioned advisory

⁵⁷⁵ Per the Guidelines for Clinical Trials: "Compliance with the requirements of the aforesaid guidelines is designed to protect the trial participants and ensure that their rights, safety and wellbeing are maintained, and that the information obtained from the study is reliable." See *Id.* at the general section.

⁵⁷⁶ Israel's Helsinki Committees serve as the medical institution's administrative arm responsible for reviewing all research proposals within its facility to ensure regulatory compliance and protection of trial participants.

⁵⁷⁷ See Public Health Regulations *supra* note 138 at §§2 - 4.

⁵⁷⁸ *Id.* at §3.

⁵⁷⁹ *Id.* at §3B.

⁵⁸⁰ Interview with MOH officials *supra* note 313.

committees' expertise. The MOH uses three Central Committees: Committee for clinical trials in drugs; Committee for clinical trials in medical devices; and the Committee for biologic cell and tissue trials. As explained by these MOH officials, these Central Committees are appointed by the MOH to provide their expert input on various scientific issues.⁵⁸¹

Ad hoc experts The MOH also uses the services of ad hoc experts for their professional input on various scientific and ethical issues. As explained by the MOH officials, the MOH may chose to obtain an expert's opinion on a default basis, i.e. where all other existing advisory committees lack the necessary expertise in the area. Furthermore, they specify that all of these Central Committees and appointed experts be comprised of hospital physicians or pharmacists. The MOH Pharmaceutical Administration's process of referring trial applications to the various professionals is exemplified in figure 5.1 below.

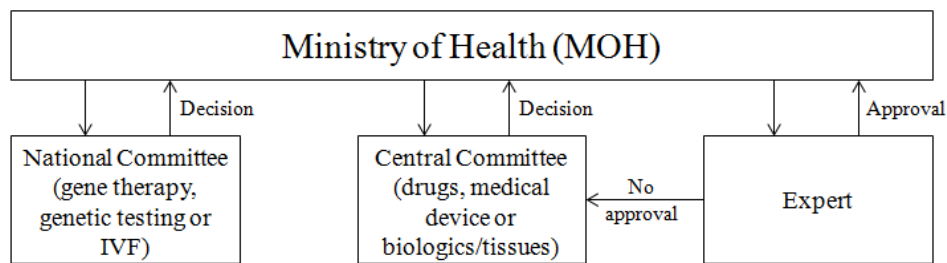


Figure 5.1: The MOH referral Process of Clinical Trial Application to Research Reviewers

1) If the trial application is in the area of the two special government advisory committees' expertise (gene therapy, genetic testing or IVF), it will be referred to one of the two National Ethics Committees for recommendations; if not, 2) the application will be referred to one of the three Central Committees depending on the nature of the trial (i.e. drugs, medical device or biologics and tissues); 3) where the application requires a very specific expertise, it will be referred to an expert. The Interviewee gave an example of a very specific oncology clinical trial seeking to study the effects of combining several approved drugs for patients' treatment; 4) the Pharmaceutical Administration can review and approve the application without referring it for

⁵⁸¹ *Id.*

further review. The example given by the MOH officials interviewed is a case where the proposed study bears no real physical risk but involves vulnerable subjects such as children.⁵⁸²

MOH officials explained that the majority of applications submitted by the hospitals for MOH review – i.e. more than fifty percent – are indeed referred to the National or Central Committees for their review and recommendations. They explained that they prefer using these advisory committees, having many professionals on board, over obtaining the opinion of an expert.⁵⁸³

For more information about the composition and responsibilities of the various research reviewers please see Chapter 3. Table 5.1 below summarizes the main differences among the different research reviewers responsible for scientific and ethical decisions. Crucial to the discussion of COI is the scope of these stakeholders’ review and authority and the COI policy and procedures as discussed in detail below. While the National Committees, Central Committees and the experts are responsible for reviewing preclinical documentation, the Helsinki committees are in addition responsible for monitoring and overseeing the conduct of the trial throughout its duration. Also, the potential COI among the members of these governmental committees and experts is governed by specific COI guidelines, as discussed below, while the institutional members are governed by the internal institution policy.

Table 5.1: Main Differences among Decision-making Committees and Experts in Clinical Trial

	National Committee (genetic and fertilization issues)	National Committee (gene therapy issues)	Central Committees	Ad hoc experts	Institutional Helsinki committee
Mandated by the Regulations	Yes, mandated for all genetic and in vitro fertilization	No, established at the discretion of the MOH.	No, established at the discretion of the MOH.	No, appointed at the discretion of the MOH.	Yes, mandated review for ‘special trial’ applications
Defined criteria for	Yes, at least 10 members,	No	Procedure only available	No	Yes, at least 7 members including 1

⁵⁸² *Id.*

⁵⁸³ *Id.*

qualification	including 2 public reps.		for committee reviewing drug applications		public rep
Appointed by	MOH Director General	MOH Director General	MOH Director General	MOH Pharmaceutical Administration	Director of institution with MOH approval
Defined legal quorum	Yes, at least 6 of which 1 public rep and 1 MOH rep	No	Procedure only available for committee reviewing drug applications	Not applicable	Yes, at least 5 of which 1 public rep, 1 physician and 1 management rep
Role	Review of scientific and ethical parameters of certain trial application	Review of scientific and ethical parameters of certain trial application	Review of toxicology, pharmacology and/or technology parameters of application	Review of various scientific or ethical parameters of trial application	Review, monitor and oversee clinical trials within the institution
COI policy	COI guidelines (discussed below)	COI guidelines (discussed below)	COI guidelines (discussed below)	COI guidelines (discussed below)	Internal institutional policy.

In sum, this section described the four key stakeholders in their roles to provide scientific, ethical and policy decisions: the institutional Helsinki committees; advisory committees; professional committees; and other experts. Overall, the scientific and ethical review of biomedical research involves multiple parties who conform to the domestic regulatory scheme as well as international standards. The primary role of these various professionals is to ensure that scientific and ethical principles are being implemented. Preclinical review and follow up oversight (particularly for institutional Helsinki committees) is part of the vital mechanism of “checks and balances”⁵⁸⁴ to make certain that the primary goals of protecting human subjects and research validity are being applied and/or strictly maintained.

Of all these decision-making professionals, two are explicitly referenced in the Public Health Regulations in their research review central role - the institutional Helsinki committees and the National Committee for genetic and in vitro fertilization issues. Contrary to other review

⁵⁸⁴ See Glass *supra* note 568 at 38.

committees, presented in Table 5.1 above, the institutional Helsinki committees are responsible not only to ensure scientific and ethical compliance at the preclinical stage, but they are also in charge of monitoring and overseeing the conduct of all their approved trials until their completion. As part of their approval and oversight mechanisms, the Helsinki committees are responsible for safeguarding the rights of human subjects against the risks of individual researchers' COI. As for the National Committee, not only do they play a significant role in the decision-making processes in reviews of certain trials, they also serve as advisors to government officials issuing their professional perspectives as a matter of government policy and guidelines.

The following sections will focus on potential COI issues that may arise in the Helsinki Committee and the National Committee. With such crucial responsibilities in mind, the section to follow discusses how COI circumstances, especially the increasing collaboration of these stakeholders with industry, may impact the Committees' primary responsibilities.

5.2 COI Challenges Objectivity of the Research Review Process

Regulatory responsibilities and obligations imposed on the research reviewers directly correlate with their vital role to safeguard the primary scientific and ethical goals of research in accordance with the regulatory regime. Such a central protective role supports the public promise that these safeguards are being implemented through the review, approval or rejection of the research proposal by "...ensuring the investigator(s) are suitable to conduct the trial, the facilities are adequate, and the methods and materials to be used in obtaining and documenting informed consent of the trial participants are appropriate."⁵⁸⁵

Generally, the research review process involves the approval of three main aspects of the trial: scientific, ethical and quality of data.⁵⁸⁶ Specifically in research review of human studies, the ethics committees must be knowledgeable of the applicable institutional, national and international laws and principles. Most prominent in Israel are the general principles of the Declaration of Helsinki. The Declaration of Helsinki incorporates specific scientific requirements to be reviewed and approved by the ethics committees, such as the requirement to

⁵⁸⁵ See Johan PE Karlberg and Marjorie A. Speers ed., *Reviewing Clinical Trials: A Guide for the Ethics Committee* (2010).

⁵⁸⁶ *Id.*

make sure that the medical research is “based on a thorough knowledge of the scientific literature... adequate lab facilities, and, as appropriate, animal experimentation.”⁵⁸⁷ In addition, the ethics committees’ review includes ethical assessment, such as assessment of the informed consent forms, or assessment of the proposed methods used to recruit the prospect trial subjects.⁵⁸⁸ No doubt, trial protocols with inadequate elements of scientific, ethical or data quality may pose risk of harm to the participants or even the public at large.⁵⁸⁹ Surely, those who are charged with the responsibility to review and approve medical research involving human subjects have difficult tasks to ensure that the rights and welfare of the human participants are being protected. With such a significant role come the inevitable demands to ensure that there are no obstacles in the way of thorough, adequate and meaningful deliberation by reviewers.

A number of issues have arisen concerning the capability of these ethics committees to perform their primary objectives. The initial concerns about the work of the U.S. IRBs (institutional review boards) were brought forward by the Office of the Inspector General (OIG) of the U.S. Department of Health and Human Services in 1998.⁵⁹⁰ The OIG report discussed the overwhelming workload pressure these ethics committees experience, preventing them from adequately performing their review duties.⁵⁹¹ The OIG further concluded that the effectiveness of the IRBs system for the protection of human subjects is in fact in jeopardy.⁵⁹² Another concern discussed by both the OIG and the literature was the lack of sufficient resources and expertise of the IRB members⁵⁹³ to conduct meaningful review of research protocols.⁵⁹⁴ Particularly for the purpose of this dissertation, are the concerns about COI.

⁵⁸⁷ See Declaration of Helsinki *supra* note 33 at §12.

⁵⁸⁸ As described by Karlberg & Speers, the goal is to ensure voluntary participation with no elements of undue influence, exploitation or coercion. See Karlberg & Speers *supra* note 585.

⁵⁸⁹ *Id.*

⁵⁹⁰ See Off. of Inspector Gen., Dep’t of Health & Human Servs., Institutional Review Boards: A Time for Reform (June 1998), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf> (last visited Sept. 7, 2012).

⁵⁹¹ The OIG report observed several IRBs meetings, and found that on an average it took two hours to review the following: eighteen initial reviews, nine expedited reviews, forty three protocol amendments and twenty one adverse event reports. The OIG concluded that based on these dense agendas, the IRBs are in fact overloaded which practically leaving very little time to truly reflect/debate on the issues. *Id.*

⁵⁹² *Id.*

⁵⁹³ Ezekiel J. Emanuel et al. discuss the deficiencies of the oversight system in several categories, one of which was the lack expertise in the science of a research study under review. See Ezekiel J. Emanuel et al, Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals, 141 *Annals Internal Med.* 141(4): 282-91 (2004).

The regulatory review and approval infrastructure creates several COI issues in view of the associations between the members of the ethic committees, sponsors, research institutions and researchers.⁵⁹⁵ Similar to the COI ascribed to the researcher, there are many potential sources of conflict for the research reviewer. The literature suggests that COI circumstances could compromise the research reviewers' ability to conduct their duties.⁵⁹⁶ Some of these COI issues are in essence identical to investigator conflicts as discussed in Chapter 4, resulting from the dual role of investigator and ethics committee member. In certain trial applications, the review and the decision of the ethics committee may have direct or indirect impact on the ethics committee member's own research work. The COI due to the dual role is becoming a significant concern as many researchers are also serving as members of influential expert committees providing recommendations for drug regulatory agencies or are involved in the development of clinical practice guidelines.⁵⁹⁷ They also perform peer review for medical journals.⁵⁹⁸

To illustrate this tension in Israel, based on MOH data⁵⁹⁹ out of the seven hospitals interviewed for this study, two hospitals have their acting chairs of the Helsinki committees also serving as the PI for clinical research funded by the industry at that same institution.⁶⁰⁰ In addition, some members of the National Committee (the government advisory committee) also serve as PI or other investigators for various medical studies. Another example which illustrates how these dual responsibilities may go to the extreme can be found in the *Dicker* case discussed in detail in Chapter 2. In this case, Dr. Dicker, then the chair of the Helsinki committee, forged dozens of documents including Helsinki committee approvals and participant informed consent forms, to

⁵⁹⁴ See Office of Inspector Gen., Dep't of Health & Human Servs., Protecting Research Subject: Status of Recommendation (April 2000), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf> (last visited on Sept. 7, 2012); also see Bowen *supra* note 340 at 557-558.

⁵⁹⁵ Bryan A. Liang & Tim Mackey, Confronting Conflict: Addressing Institutional Conflict of Interest in Academic Medical Centers, 36 Am. J. L. and Med. 136 (2010)

⁵⁹⁶ See for example Sharona Hoffman & Jessica Wilen Berg, The Suitability of IRB Liability, 67 U. Pitt. L. Rev. 365.

⁵⁹⁷ See Lemmens *supra* note 29 at 752.

⁵⁹⁸ *Id.*

⁵⁹⁹ See the MOH's Committee for Contracts with Commercial Companies, Medical Research Conducted by Investigators during 2009 Compared to 2006-2008 (In NIS), (September 6, 2010) (unpublished report) (on file with Author).

⁶⁰⁰ The MOH data stipulate that in 2009 the two chairs proposed industry sponsored research budget for the total amount of ~NIS 1.5 million (approximately U.S.\$ 375,000). *Id.*

support his fictitious clinical research.⁶⁰¹ As the chair of the Helsinki committee, Dr. Dicker had access to documentation, and was able to issue forged approvals on behalf of the committee after the fact. This is not to say that a member of ethics committee serving as investigator is wrong and will cause research misconduct. The purpose of these examples demonstrates how the dynamics of these two roles may cause COI concerns which escape attention in the regulations.

Another COI concern relates to issues of allegiance between the research reviewers and their peers.⁶⁰² Often times the PIs are colleagues of the ethics members working for the same institution. Protocols submitted by close colleagues or department members raise allegiance issues that may increase the potential for biased decision-making. This can be especially worrisome if the research protocol is submitted by a higher ranking employee to be reviewed by a lower ranking employee. Such circumstances may rise concerns about potential coercion or the fear of reprisal in protocol review and approval.⁶⁰³ Research reviewers may be reluctant to disapprove of their colleagues' proposals. Indeed, studies in the U.S. suggest that IRBs rarely deny research applications.⁶⁰⁴

Some scholars argue that the U.S. IRBs' bias toward approving research applications may also result from the position of the reviewer within the research institution. For example, in situations where a reviewer feels obligated to help promote the research at the institution in which he works.⁶⁰⁵ Generally, the decentralization of review and monitoring responsibilities as delegated to medical institutions has advantages. The concept of local institutional review was thought to be favorable since local institutions are in the best position to be familiar with the specific investigators and the local community from which prospective participants can be drawn.⁶⁰⁶ On the downside, however, there is a built-in COI: on one side, is the objective to protect the

⁶⁰¹ See the Dicker case *supra* note 38.

⁶⁰² See Hoffman & Berg *supra* note 596.

⁶⁰³ See Bowen *supra* note 340 at 553.

⁶⁰⁴ Hoffman & Berg argue that studies show that instead of rejecting trial protocols, U.S. IRBs tend to allow the constant revisions of protocols. See Hoffman & Berg *supra* note 596.

⁶⁰⁵ *Id.*

⁶⁰⁶ See Marjorie A. Speers, Evaluating the Effectiveness of Institutional Review Boards in *The Oxford Textbook of Clinical Research Ethics*, 560 (Emanuel E. at el. ed. Oxford 2008).

primary goals of research – especially safeguarding the trial participants – and on the other side is the obligation to the employer institution.⁶⁰⁷

Additionally, as discussed in detail in Chapters 2 and 4, in view of the increasing dependency on private sources of research funding, along with the increasing pursuit of profit and commercial avenues, additional financial interests have been introduced. Given these strong financial incentives and entrepreneurial opportunities, it is not surprising that the need for an independent evaluation process conducted by unbiased reviewers has become even more evident.⁶⁰⁸ Some commentators argue that with the increasing commercial sponsorship and the growing financial incentives for research institutions to obtain revenues from their research comes an increase in the conflicting interests which compromise the institutional reviewers' mission to safeguard the principles of research.⁶⁰⁹ In Israel, hospitals generate revenues from clinical trials by the biomedical industry which contributes significantly to the hospitals' operations including acquiring state of the art medical equipment and hiring experienced medical staff.⁶¹⁰ These crucial institutional interests may have an impact on the decision by the employees of such institutions. This tension may also be intensified in Israel particularly in view of the regulatory requirement to have a representative of the hospital management on every Helsinki committee meeting.⁶¹¹

As discussed in Chapter 4, Shamo and Resnik argue that the concerns of COI are that it can undermine integrity. They argue that COI can undermine integrity by impacting the person's thoughts, motivation and behaviors.⁶¹² They state that COI circumstances may include situations in which the conflicted person is capable of making a sound judgment, but fails to implement it due to the conflicting interests.⁶¹³ The inherent tension arises from the unclear, and even confusing, role of the members of the ethics committee working in the institution in terms of allegiance. This tension relates to the two responsibilities of members of the Helsinki

⁶⁰⁷ *Id.*

⁶⁰⁸ See Glass *supra* note 568 at 37-38.

⁶⁰⁹ Mary R. Anderlik and Nanette Elster, *Lawsuits Against IRBs: Accountability or Incongruity?* 29 *J.L. Med. & Ethics* 220 (2001). See also the 2000 OIG report *supra* note 594.

⁶¹⁰ See Hochman et al. *supra* note 149.

⁶¹¹ See the Public Health Regulations *supra* note 138 at §1, Second Appendix.

⁶¹² See Shamo & Resnik *supra* note 14 at 190-191.

⁶¹³ *Id.*

committees. These two responsibilities, protecting the trial participants and protecting the goals of the institution may conflict. The challenge for these employees is to find a way to maintain their objectivity to implement their primary protective goals, while at the same time maintaining the institution's support by not impeding the progress and commercialization of new technologies.

As opposed to rich and reliable empirical research and scholarly material regarding the work of the ethics committees (IRBs) in the U.S., very little data exist on the processes, procedures and policies of the members of Israel's institutional ethics committees and the government advisory committee - National Committee. Concerns about whether the ethics review system is well-equipped to safeguard the primary goals of human research were initially brought up in 2004 by the Israeli State Comptroller.⁶¹⁴ The State Comptroller published incriminating findings that highlighted serious ethical and procedural deficiencies with respect to the institutional Helsinki committees in several prestigious hospitals, and one regarding the National Committee.⁶¹⁵ The following inter alia incidents were reported regarding the institutional Helsinki committees audited:

- a) In many cases the institutional Helsinki committees were but 'rubber stamps', approving all research applications with no oversight, or in some cases without conducting any meeting at all,⁶¹⁶
- b) In several cases the committee members approved protocols of their own studies;⁶¹⁷
- c) In two hospitals, the public representative members of the committees were affiliated with the hospitals.
- d) In several cases of death to participants, the PI failed to report the deaths to the Helsinki committee⁶¹⁸; even upon notification to the committee, in many cases the Helsinki committee failed to report it to the MOH as required.⁶¹⁹

⁶¹⁴ The Israeli State Comptroller, usually a retired judge, is appointed by the President with the recommendation of the Israeli Parliament (the Knesset) and is responsible by law for reviewing, investigating and supervising government agencies' and public institutions' policies and operations. The State Comptroller's findings are brought to the investigated bodies, the Knesset and the public. More information is available at <http://www.mevaker.gov.il/serve/site/english/index.asp> (last visited Sept. 7, 2012).

⁶¹⁵ State Comptroller's Report *supra* note 36.

⁶¹⁶ The State Comptroller found that in the first hospital the trial applications were approved by the committee without conducting any meetings; in the second hospital there were no protocols for the meetings and in the third hospital the protocols had no reasoning for decisions. *Id.*

⁶¹⁷ The report indicated that these cases are basis for concerns for COI. *Id.*

- e) In one hospital the chair of the Helsinki committee temporarily approved trial applications with no discussion of the full committee, in some cases three weeks or more before the committee meetings.
- f) In some cases, essential information about the trial was not included in the approved informed consent forms;⁶²⁰
- g) During 2001 - 2003 the majority of the trial applications were defined by the Helsinki committee as “special trials” (in cases of “special trials” the application does not require the approval of the MOH); while a third of the cases should have been defined as “non-special trials” requiring the approval of the MOH.⁶²¹

With regard to the National Committee (government advisory committee), the State Comptroller found that at the time, contrary to the Public Health Regulations, there were no public representatives serving on the committee.⁶²² Lastly, the report found lack of adequate oversight by the MOH of the activities of the Helsinki committees.⁶²³

In 2005, two joint parliamentary committees of the Israeli Knesset commenced an urgent discussion on the State Comptroller report’s findings.⁶²⁴ During the discussion, the chair of the parliamentary committee, Mali Polishok-Bluch, was appalled by the situations mentioned in the report where the PI was also serving as a member of the committee approving its own trial.⁶²⁵ Lea Ness, the Chair of the Science and Technology committee at the time, indicated in response that she was told that due to the fact that those who serve on the various ethics committees “are the best people” [Translated from Hebrew], they might be involved in the approval of their own research agendas.⁶²⁶ Other mentioned that the solution would be to have detailed procedures and

⁶¹⁸ The Guidelines for Clinical Trials require the PI to report of any incident involving death to participants to the Helsinki committee within 48 hours. See the Guidelines for Clinical Trials *supra* note 35 at §15.1.2.1.

⁶¹⁹ The Guidelines for Clinical Trials requires the Helsinki committee to investigate any death incident to participants and to report its findings to the MOH within 7 days. *Id.*

⁶²⁰ See the State Comptroller report *supra* note 36.

⁶²¹ *Id.*

⁶²² Per the report, in a response letter from December 2004, the Director-General stated that he will work to correct that and appoint public representatives to the committee. *Id.*

⁶²³ *Id.*

⁶²⁴ See the Joint meeting of the State Audit Comm. & the Science & Technology Comm., protocol no. 228 (November 7th 2005) available at <http://knesset.gov.il/protocols/data/html/mada/2005-11-07.html> (Isr.) (last visited Sept. 7, 2012).

⁶²⁵ *Id.*

⁶²⁶ *Id.*

guidelines⁶²⁷, and another talked about the need for the MOH to allocate proper budgets for monitoring and oversight.⁶²⁸ Distinct from several additional Knesset discussions, which led to the revisions of the MOH guidelines, the State Comptroller's damaging report also spurred numerous news reports, and ultimately several private⁶²⁹ and government bills initiating new legislation. To date, no additional legislation has passed.

In sum, the regulatory system relies on the research reviewers to safeguard the principles of research. A number of incidents have raised concerns about the ability of these ethics committees to perform their primary objectives both in the U.S. and Israel. Among these concerns are the risks of COI resulting from the research reviewers serving as researchers for studies conducted at the same institution in which they are employed. In addition, the relations between the ethics committee members and their peers also causes concerns for COI, as often they are professional colleagues working for the same institution. Lastly, the increasing commercial sponsorship and the growing financial incentives for research institutions also increases the risks for conflicting interests. The challenge for these professionals is to find a way to maintain their objectivity to implement their primary protective goals, while at the same time maintaining the institution's support without impeding the progress and commercialization of new technologies. Concerns for COI at the reviewers' level, as scholars warn, may foster lack of functional autonomy which ultimately creates biases in a reviewer's ability to produce decisions promoting the best interests of the trial participants.⁶³⁰

5.3 Managing Research Reviewer COI under the Israeli Regime – Regulatory and Policy Mechanisms

In view of the regulatory responsibilities carried out by the Helsinki committees and the National Committee, the concerns for their integrity and impartiality cannot be overstated. In the U.S., for example, the federal regulations issued by the FDA mandate recusal of committee member with

⁶²⁷ See Dganit Shai's comments *Id.*

⁶²⁸ *Id.* by Lea Ness.

⁶²⁹ Private Bills are presented by a member of the Knesset or a group of Knesset members, as oppose to government bills which are presented by a minster member of the acting government.

⁶³⁰ See Liang & Mackey *supra* note 595.

COI from participating in any IRB (Institutional Review Board) review.⁶³¹ As discussed in Chapter 7, the U.S. federal regulations also address potential COI in its government agency advisors. The question of the appropriateness of the collaboration between industry and U.S. FDA advisors came under increased public scrutiny. The concerns resulted from the high number of outside FDA advisors who were found to have financial ties with the industry they scrutinize.⁶³² This collaboration raises concerns about the potential for bias⁶³³ and may undermine the public's trust in the review process.⁶³⁴ As a result, in 2007 the then President George W. Bush signed into law the Food and Drug Administration Amendments Act of 2007⁶³⁵, which established stricter rules safeguarding against COI in the members of the FDA advisory panels, and required public disclosure of the identified COI onto the FDA website.⁶³⁶

In Israel, as opposed to COI ascribed to individual researchers, the regulatory regime does not formally address potential COI of the members of the institutional Helsinki Committee. The Public Health Regulations, however, do require the Helsinki committees (as well as the National Committee – the government advisory committee) to include public representatives as full members with regular voting authorities. With regard to COI ascribed to members of the National Committee, or any other government advisory committee and ad hoc consultants for that matter, a specific MOH Director-General guideline for COI disclosure and management applies. In addition, other general statutory provisions applicable to government employees may also apply. Below are the relevant mechanisms applicable to various COI issues specifically with regard to the Helsinki and the National Committees.

⁶³¹ 21 CFR 56.107(e) states: “No IRB may have a member participate in the IRB’s initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.”

⁶³² Studies show that twenty eight percent of FDA advisors who participate on FDA advisory panels have financial or other relations with the industry their review. For more information see Peter Lurie et al., Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings, *JAMA*. 2006; 295(16):1921-1928.

⁶³³ Lurie et al study showed that seventy three percent of 221 advisory committee meetings between 2001 and 2004 included at least one member with a disclosed financial COI, while only one percent of whom were recused. *Id.*

⁶³⁴ Shamoo & Resnik *supra* note 14 at 284-285.

⁶³⁵ Food and Drug Administration Amendments Act, 18 U.S.C. §712(c)(2)(B) (2007).

⁶³⁶ These included recusal of any advisory panel members from taking part in the discussion and voting if they have a financial interest in the particular matter unless they were given a waiver. Also, the new rules requires the FDA to disclose these identified COI or, if applicable, the reasons for granting a waiver. *Id.* at §712(c)(2) and 712(c)(3) respectively.

5.3.1 The MOH Director-General COI Guidelines from 2009 – Applicable to All Government Advisory Committees and Experts

In March 2009⁶³⁷ the then MOH Director-General, Avi Israeli, issued specific guidelines for COI and protection of privacy of information applicable to any member of the National Committees, Central Committee or experts who provide their professional opinion to the MOH (“COI Guidelines”).⁶³⁸ The COI Guidelines define the advisors who provide their opinion to the MOH broadly as “every person that is not a MOH employee who serves, whether with consideration or without, as a consultant, committee member or opinion provider to each of the ministry’s units.”⁶³⁹ [Translated from Hebrew] The goal of the COI Guidelines was to be able to: “...neutralize the risks of COI”⁶⁴⁰ [translated from Hebrew] of all the professionals providing opinions to the MOH by virtue of revealing their conflicting interests.

The COI Guidelines acknowledged the general COI doctrine, adopted by the Israeli Supreme Court discussed in detail in Chapter 2, which stipulates that any individual conducting administrative functions is prohibited from being in COI circumstances.⁶⁴¹ It also acknowledged the judicial approach, asserting that the goal is to minimize the situations which would cause reasonable persons to believe that a decision maker’s judgment has been wrongly influenced, whether or not it actually has.⁶⁴²

The COI Guidelines explicitly state that if the conflicting interest is continuous and central to the matter of the opinion, there will be no other way but to require this conflicted individual to abstain from serving as a government advisor to the specific matter.⁶⁴³ The COI Guidelines explicitly recognize the valid concern, originally raised by Judge Strasberg-Cohen in the

⁶³⁷ The relatively new MOH COI Guidelines were a direct result of the Attorney General guidance from 2006. This 2006 guidance, requires the different government ministries to regulate current public officials or newly nominated officials. The ministries, or the Attorney General, were required to review and issue an arrangement with each public official which will address their various COI. See The Attorney General Guidance *supra* note 135. The guidance states that the individual has the responsibility to avoid being in COI, as well as to report back to the Attorney General if the circumstances relating to COI have changed.

⁶³⁸ See the Director General of the Ministry of Health Notice, 14/09 (2009) (Isr.), available at http://www.health.gov.il/hozer/mk14_2009.pdf (last visited Sept. 7, 2012).

⁶³⁹ *Id.*

⁶⁴⁰ *Id.* at §5.

⁶⁴¹ See Barak-Ereaz, navot & Kremnitzer *supra* note 96.

⁶⁴² See COI Guidelines *supra* note 304 at §3.

⁶⁴³ *Id.* at §6.

Pachima case⁶⁴⁴, in which the COI doctrine to disqualify the eligibility of public official, should be applied carefully in order not to deter honest and talented people from roles they are suitable for.⁶⁴⁵

In order to assess the possible COI, the COI Guidelines require the different advisors (those who are currently in office or new nominees) to sign a non COI declaration, and disclose information in a detailed questionnaire, attached as appendices to the Guidelines.⁶⁴⁶ The five page questionnaire, attached as Appendix 2 to the COI Guidelines, requires information inter alia, about the following: the member's jobs and duties within the last four years, any directorate membership in various public and nonpublic companies, stock ownership or for-profit partnerships (for the member or his or her relatives⁶⁴⁷), or any other responsibilities (either of the member or his or her relatives) that might put them in risk for COI. The advisors and nominees are also required to sign a COI declaration, Appendix 1 to the Guidelines, in which they declare, inter alia, that apart from the information they disclosed in the questionnaire, they do not have other matters that might put them in COI circumstances.⁶⁴⁸ By signing the COI declaration, the advisors or nominees are committed to report to the committee coordinator any case where personal interest (whether direct or indirect) exists in the matter of the opinion requested, following which they will not be involved in preparation of the opinion (whether directly or indirectly).⁶⁴⁹ The members are also required to notify the committee coordinator of any change in their COI status which may influence them in their role as government advisors.⁶⁵⁰ Nevertheless, the COI Guidelines do not provide a definition to COI.

⁶⁴⁴ See the *Pachima* case *supra* note 107, also see H CJ 1045/89 *Yaakov Daniel v. The Mayor of Kiryat Ata*, 44(3) PD 157 [1990] (Isr.).

⁶⁴⁵ See COI Guidelines *supra* note 304 at §6.

⁶⁴⁶ The COI Guidelines distinguish between the different professionals by virtue of their services they provide to the MOH. Briefly, §8 discusses the responsibilities of the members of the National Committees which provide the MOH ongoing professional opinions; §9 discusses the responsibilities of one time advisors which their opinion have influential weight over the MOH decision-making; and §10 various advisory committees where in general their opinion has no influential weight over the MOH decision-making.

⁶⁴⁷ "A relative" was defined in the questionnaire as a spouse, parent, child or other dependents. See *Id.* at the Appendix 2 §5.

⁶⁴⁸ *Id.* at Appendix 1 §4.

⁶⁴⁹ *Id.* at the Appendix 1 §6.

⁶⁵⁰ *Id.* at the Appendix 1 §7.

After reviewing the answers to the COI questionnaire, the relevant committee coordinator (MOH official), in consultation with the MOH legal department, has the following options:

- 1) To determine that there is no risk of COI, and to accept the nomination or the professional opinion.
- 2) To determine that there is a risk of COI, in which case they can either:
 - a. Disqualify the nomination or opinion; or
 - b. Accept the nomination or opinion subject to restriction as they deem fit.⁶⁵¹

In cases where the MOH officials did find COI but believe that there is crucial importance in allowing the conflicted expert to be part of the discussion or decision-making process, as no one with the same expertise exists, then the MOH official can consult with the Deputy Attorney General. If the Deputy Attorney General approves such a nomination, then this conflicted advisor will be allowed to participate and to provide their professional opinion.⁶⁵² In cases where COI was found but the MOH officials decided to let the conflicted advisor be part of the decision-making process, the former are responsible to notify the chair of the relevant advisory committee, while the chair is responsible to notify the other members.⁶⁵³ The committee members will be notified about the affiliation without disclosing its type. This process will take place at the beginning of each committee meeting when such COI is relevant to the specific discussion.⁶⁵⁴

In sum, the COI Guidelines required detailed disclosures and include a process for identifying and managing COI of the various MOH advisors, and impose the task of review and enforcement upon the committee coordinator as well as the MOH's legal department.

The MOH official interviewed⁶⁵⁵ indicated that the MOH underwent a process, in which all the existing members of the National Committees were required to fill out the mentioned

⁶⁵¹ *Id.* at §16.

⁶⁵² *Id.*

⁶⁵³ *Id.* at §18.

⁶⁵⁴ *Id.* at §18.

⁶⁵⁵ Interview with MOH official *supra* note 177.

questionnaire.⁶⁵⁶ It was a decision to begin organizing the nomination processes for government advisors, and to screen those from whom the MOH seeks opinions. This official stated that in the beginning of the process, several officials in the MOH were concerned about how the respective members of the National Committee would react to such disclosure demands, but emphasized that all the members were in fact very cooperative and had filled out the COI questionnaire.⁶⁵⁷

On the face of it, the COI Guidelines provide a very detailed process of disclosure and review of COI to all who serve as advisors to the MOH. However, these Guidelines fail to explicitly define what constitutes COI, and do not provide clear standards to the MOH officials on how to assess or manage it once it has been identified. This difficulty was manifested in the interview conducted with the official from the MOH, discussed in detail in section 5.4 below.

5.3.2 *The Public Representatives*

The Public Health Regulations require the Helsinki committee to be comprised of at least seven members, one of whom must be a legal professional or religious person.⁶⁵⁸ The Public Health Regulations also requires the National Committee to be comprised of at least ten members, one of whom must be a legal professional or religious person.⁶⁵⁹ These regulatory requirements allow members of the public to participate in this important national or institutional decision.

Arguably, public participation in government advisory decisions can enhance the credibility of the decision, and improve the committees' perspectives on the relevant issues.⁶⁶⁰ For example, the U.S. Institute of Medicine (IOM) in 2002 issued a report in which it emphasized the importance of transparency and the necessity to maintain interaction with the public.⁶⁶¹ The IOM report stated: "It is difficult to justify denying the public knowledge about existing research, particularly if it is publicly funded. Even in the context of classified research sponsored or

⁶⁵⁶ This official mentioned that this process was a direct result of the State Comptroller actively and continuously checking if all the government agencies are implementing the 2006 Attorney General Guidance for COI. See the 2006 Attorney General guidance *supra* note 135.

⁶⁵⁷ Interview *supra* note 177.

⁶⁵⁸ See the Public Health Regulations *supra* note 138 at §1, Second Appendix.

⁶⁵⁹ *Id.* at §1 Third Appendix.

⁶⁶⁰ See Daphne Barak-Erez *supra* note 96 at 218.

⁶⁶¹ See D. Federman, D., Hanna, K.E. & L.L. Rodriguez, Responsible research: a systems approach to protecting research participants (National Academies 2003).

funded by the government, the protection of Research Ethics Review Board (REB) review [similar to the IRB] should be provided. Secrecy often has led to abuses of human rights.”⁶⁶²

Arguably, allowing a public person, not affiliated with the research community, to take part in the Helsinki committee and National Committee decisions, creates a more balanced community perspective of the research process.⁶⁶³ Some argue that requiring more community representation in research review is crucial to achieving a successful system of protection to human participants. One states that these public representatives are better equipped to advocate for the rights of the research participants in light of their inner knowledge and approach toward the risks and benefits of research in general.⁶⁶⁴

In order to be able to advance their primary goals, featuring nonaffiliated members in the committee requires a structured training process to ensure that these members fully understand their regulatory responsibilities.⁶⁶⁵ As stated by a member of the National Committee interviewed, from time to time they organize conferences with specific objectives to educate their nonscientific members.⁶⁶⁶

Daphne Barak-Erez, a well known Israeli legal scholar, warns however that placing nonaffiliated members in administrative committees may also allow undesired biases. She argues that with no specific nomination criteria for these public representatives, their placement on the committee will not ensure balanced representation. In addition, Barak-Erez argues that even when the provision does identify criteria for representation it does not determine the procedures for finding these representatives.⁶⁶⁷ The State Comptroller report (discussed in section 5.2 above), reinforces some of Barak-Erez’s concerns: COI issues were found where the public representatives in some of the Helsinki committees were found to be affiliated with the hospitals. The tension between competency and objectivity for government advisors is discussed in detail below.

⁶⁶² *Id.*

⁶⁶³ See Bowen *supra* note 340 at 557.

⁶⁶⁴ *Id.*

⁶⁶⁵ *Id.* at 557-558.

⁶⁶⁶ Interview with National Committee member *supra* note 312.

⁶⁶⁷ See Daphne Barak-Erez *supra* note 660 at 218-220.

5.3.3 *The Declaration of Helsinki COI Provision*

The Declaration, written by the World Medical Association, defines a set of ethical principles as the basis of a moral code for medical researchers. The Declaration relies primarily on the oversight of an independent ethics board to safeguard the scientific and ethical requirements for human subject protection. Israel's regime explicitly adopted the Declaration's provisions.⁶⁶⁸ In fact, Israel's regulations use the name "Helsinki" Committees for their ethics boards, emphasizing the strong connection between this ethical framework and its processes and practices.

The Declaration acknowledges the risk of COI at the level of members of ethics committee when it defines the role of these members. As per the Declaration: "This committee must be independent of the researcher, the sponsor and any other undue influence."⁶⁶⁹ The research reviewers are designed to fulfill the central role of independent and formally designated review of medical research to ensure the rights and welfare of human participants are protected and to safeguard the integrity of scientific data produced by scientific research. The Declaration requires elements of independence on the part of ethics committees in order to allow adequate oversight processes. The Declaration also recognizes a general duty of disclosure to the trial participants of any potential COI, namely "...each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, and institutional affiliations of the researcher".⁶⁷⁰

5.3.4 *General COI Rules Applicable to All State Employees*

As discussed in detail in Chapter 2, all public officials must be mindful of COI general regulations in all aspects of their public work.⁶⁷¹ In essence, the COI doctrine follows the position and not the individual.⁶⁷² There are general COI provisions that apply to state employees, including those who serve on the Helsinki committees and National Committees. Typically when a public official breaches the COI rule, it is regarded as a disciplinary violation.

⁶⁶⁸ The Guidelines for Clinical Trials explicitly state that: "Any clinical trial, including the planning, approval, conduct, recording, and reporting thereof shall be carried out in due compliance with the principles of the Helsinki Declaration. ..." See Guidelines for Clinical Trials *supra* note 35 at general section.

⁶⁶⁹ See §15 of the Declaration of Helsinki *supra* note 33.

⁶⁷⁰ *Id.* at § 14.

⁶⁷¹ HCJ 5734/98 *Tzadok Azriel and others v. Israel Land Council Subcommittee* 55(5) PD 859, 865 [1999] (Isr.).

⁶⁷² See Zamir *supra* note 72.

Section 43.021 of the Civil Service code, for example, stipulates that a state employee cannot serve as a member of a corporate board, if this might conflict with his or her public service work or obligations. In these circumstances, breaching the COI rule will entail disciplinary action based on section 17(2) to the State Public Services (Disciplinary) Law from 1963. Section 3 of the Civil Service (Gifts) Law 1979 imposes fines in the event that a public servant fails to disclose a gift he or she received and failed to act in accordance with the provisions of the law.⁶⁷³ This statute was explicitly extended not only over physicians working in government hospitals but also in other public hospitals. The Law aims to prevent the perception that the gift or benefit was given in order to create bias.

Other provisions stipulate that a state employee taking actions that constitute COI can be regarded as guilty of inappropriate behavior under §17(c) of the State Service (Discipline) Law 5723-1963. Notably, ethics committee members working for state owned hospitals, are state employees under the law, and thus are subject to these provisions. Violation of this law may trigger disciplinary proceedings against the employee in the State Employees Disciplinary Tribunal.

In sum, in order to protect against the risks of COI the Israeli regime incorporates several mechanisms, some of which apply only to government advisors and some to the institutional Helsinki committees. The most relevant is the COI Guidelines issued by the Director-General of the MOH, imposing detailed disclosure upon government advisors and COI management processes enforced by the MOH officials. Other mechanisms are the requirement that public representatives to be part of the ethics committees, and general COI provisions applicable to research reviewers by virtue of their role as public officials.

This brief review of the scholarly literature and COI regulatory mechanisms has served to highlight a number of issues relating to the definition and use of the concept of COI at the research reviewers' level in the realm of medical research involving human participants. Subsequent to the regulatory framework overview, the following discussion is devoted to

⁶⁷³ The fine will be three times the value of the gift/benefit.

exploring how these mechanisms were put into play by the relevant stakeholder based on interview data.

5.4 Defining and Applying the COI Doctrine to Research Reviewers

The following section focuses on the data obtained from hospital professionals, members of the National Committee and MOH officials, who are in charge of defining, identifying and managing and/or eliminating research reviewers' COI. As discussed in the methodology section in Chapter 1, all interviewees were asked to articulate their experiences in the following thematic areas: how they define and identify COI at the ethics committee level; and what actions are taken once COI is identified. To control the interviewees' potential bias and to strengthen the internal validity of this research, the goal was to interview several professionals from each committee.

Generally, all interviewees taking part in scientific and ethical review expressed a high level of commitment to safeguarding human participants' safety and health. All interviewees were in agreement that the dual responsibility of investigator serving as ethics members causes concerns for COI and bias. At the institutional level, other layers of potential COI, such as familial or commercial, were not addressed by the hospital officials. Furthermore, differences between the institutional reviewers and the government advisors reviewers were found regarding the scope and definition of COI. Particularly with government advisors, inconsistency was found among the interviewees with regard to their definition to what constitutes member COI. Contrary to the inverse correlation found in Chapter 4, the interview data reveals a direct correlation between the scope of the definition of COI and its consequences. In accordance with the thematic approach to the interviews, the following sections are divided into three: general information about the various committees' role and functions; COI definition and identifying processes; and consequences of COI.

5.4.1 Research Reviewers' Decision-making Processes

As described by the interviewees, the Helsinki committees and the National Committee typically meet once a month for a few hours. The interviewees explained that since the vast majority of these committee members are senior professionals having other responsibilities within the institutions or in other facilities, they are not able to meet more than once a month. The members of the Helsinki committees interviewed were asked to estimate how many new applications are

being reviewed in each monthly meeting. As anticipated the number of the trial application submitted and reviewed mirrors the size of the hospital. While the medium size hospital in the sample averages review of 15-20 new trial applications per month, the other six bigger size hospitals in the sample estimated an average between 30 and 50 a month. The National Committee members indicated a review of 100 to 140 new applications per meeting.⁶⁷⁴

In the Helsinki committees, the interviewees explained that there are no veto rights for any member in the committee regardless of their position within the institution. They all described a somewhat similar decision-making process in which on only rare occasions did they have to conclude with a vote. Typically they come to an agreement together whether to approve, approve with amendments, or deny the application. One interviewee remembered one rare occasion where they had to indicate in the committee's minutes that a certain member disapproved.⁶⁷⁵ Another interviewee in a different hospital explained that he remembers two cases where the committee could not reach an agreement, and they decided to deny the application.⁶⁷⁶ All the members of the Helsinki committees interviewed indicated many cases where they asked the PI for more clarifications; some indicated that in certain circumstances the committee would ask the PI to appear before the committee to present his or her applications and clarifications.

With regard to the National Committee, its members interviewed clarified that "it is a process." [Translated from Hebrew] They explained that now, for example, they are discussing the sensitive issue of behavioral genetics. The interviewee indicated that this is a sensitive area because lay persons are not well informed about it. Therefore, the National Committee chair initiated a seminar for all the National Committee members, in order to provide them with the required information to make informed decisions. Similar to the Helsinki committees, the interviewee indicated that there are no veto rights in the committee and they hardly ever vote on a trial.⁶⁷⁷ He further clarified that "the purpose is to create a process to allow appropriate healthy decision making, in order to negate any feelings that members were ignored."⁶⁷⁸ [Translated from Hebrew] As indicated, the majority opinion usually governs, and if reservations are raised

⁶⁷⁴ Interview with National Committee member *supra* note 435.

⁶⁷⁵ Interview with hospital 2 official *supra* note 436.

⁶⁷⁶ Interview with hospital 4 official *supra* note 466.

⁶⁷⁷ Interview *supra* note 312.

⁶⁷⁸ *Id.*

by public reps, then sometimes they will ask that it be noted in the minutes.⁶⁷⁹ However, as indicated by all the interviewed members, their committee usually comes to a compromise. Similar to the Helsinki committees, the National Committee may require the PI to provide more information or to comment on the issues raised.⁶⁸⁰

5.4.2 Defining and Identifying Committee Member COI

Helsinki Committees Contrary to the inconsistency found in defining COI at the individual investigator level discussed in Chapter 4, a wide consensus was found among the interviewees on what constitutes COI at the Helsinki committee member level. All the hospital officials interviewed agreed that a member of the ethics committee who is also serving as the investigator of the research application reviewed will be in COI circumstances. In other words, the dual responsibility of ethics reviewer and trial investigator will be regarded as a COI situation. As for the mechanism for identifying this dual role, all the hospital officials indicated that the investigator involved in research is disclosed within the application forms. As discussed in Chapter 4, the investigators - whether PI or other investigators- taking part in the clinical trial are listed in the new clinical trial application forms.

Except for two interviewees, other hospital officials interviewed did not mention other possible associations such as familial or commercial as a concern for COI. These relations may include familial relations with the applicant or contractual relations with the specific sponsor or competitor or even the investigational product. These associations are definitely not theoretical as they are in fact regarded by the MOH Director-General as concerns for COI which require disclosure and COI management but only at the government advisor level. As mentioned above, the MOH COI Guidelines from 2009 require broad disclosure of various potential associations such as familial, commercial and entrepreneurial interests. Having said this, the mandatory disclosure requirement is only applicable to the members of the government advisory committee, and never includes the members of the institutional Helsinki committee. As one might argue, by virtue of their role as government advisors they should be required to adhere to a higher level of integrity and objectivity compared to the institutional actors – the Helsinki committee members. Thus, based on the lack of any specific disclosure requirement upon the institutional reviewers, it

⁶⁷⁹ *Id.*

⁶⁸⁰ Interview *supra* note 312.

is then reasonable that the hospital officials interviewed never really addressed these additional associations as COI concerns.

The hospital officials, similar to individual investigator's COI, indicated that they never proactively initiate COI review for the members of the committee. Hospitals in practice manage the ethical issues related to COI internally. They expect their employees will be loyal to the goals of the institution. Essentially, all hospital officials in one way or another indicated that they strongly rely on the integrity of the Helsinki committee's members. One interviewee in hospital 3 stated: "We are all serious and responsible professionals. You can't trust a doctor - a member of the committee - to treat a patient and not trust them with medical research."⁶⁸¹ [Translated from Hebrew] Another interviewee stated: "The assumption is that the Helsinki committee is very appreciative and respectful to the integrity of its members".⁶⁸² [Translated from Hebrew]

Two interviewees reflected their opinion regarding potential COI where the member of the Helsinki committee had a supervisory role over the PI or the study. These two interviewees – from hospital 2 and 4 – in fact held opposing views. The Interviewee from hospital 2 found this supervisory role problematic indicating: "Since we use reviewers in the committee to review certain research applications within their area of expertise, they will usually be in the same department where the PI works. This may also create COI. This is part of the given circumstances where the committee members are also researchers themselves."⁶⁸³ [Translated from Hebrew] At the same time, the interviewee from hospital 4 could not find any problem with these circumstances. On the contrary, this interviewee explained that with a supervisory position such as chief physician in the applicant department, the member of the ethics committee will have more understanding of the research at hand to enable him or her to contribute to the discussion and deliberations.⁶⁸⁴ As will be discussed below, the same circumstances were discussed by the interviewee from the National committee.

⁶⁸¹ Interview with hospital 3 official, in hospital 3 office, Israel (September 14th, 2010).

⁶⁸² Interview *supra* note 436.

⁶⁸³ *Id.*

⁶⁸⁴ Interview *supra* note 466.

National Committee With regard to defining COI for the members of the National Committee, the interviewees drew a broader definition of what would be considered COI circumstances. The member of the National Committee interviewed stated that in their committee they have many members who are active researchers themselves involved in developing various biomedical technologies. These members approve technologies which may be in competition to their own.⁶⁸⁵ The interviewee stated that COI is obvious in circumstances where the member of National Committee is connected “in way one or another” [Translated from Hebrew] to the application in question. This interviewee found obvious COI circumstances where there are familial relations between the member and the applicant, or when the member serves as the chief physician in the same department as the applicant. This interviewee remembered a case where a COI situation was brought to the attention of the committee and was managed in which the member’s husband was the head of the genetics department in the hospital and the PI.⁶⁸⁶

The questions arise as to how far these relational associations between the member and the subject matter should go. The MOH official stated that drawing the lines of what constitutes COI is very difficult. She gave an example where a member of the National Committee had a grandson who suffers from autism. She wasn’t sure whether or not this member was indeed in COI circumstances whenever the application discussed issues of autism. She did mention that in her opinion, regarding these circumstances as COI seems to go too far. She was also unwilling to acknowledge COI circumstances where the applicant is from the same hospital as the National Committee member.⁶⁸⁷ Another interviewee from the MOH disagreed and suggested that indeed applicants from the same hospital as the committee member should be a concern for COI.⁶⁸⁸

As for the process of identifying potential risks for COI, the MOH officials interviewed stated that all the members of the National Committee were required to fill out a questionnaire for COI per the MOH Director-General’s 2009 Guidelines discussed above. They were required to provide information about whether they serve as an adviser or representative for the industry.⁶⁸⁹ The COI Guidelines impose a COI screening upon the committee’s coordinator. As the National

⁶⁸⁵ Interview *supra* note 435.

⁶⁸⁶ *Id.*

⁶⁸⁷ Interview *supra* note 185.

⁶⁸⁸ Interview *supra* note 177.

⁶⁸⁹ Interview *supra* note 313.

Committee official interviewed explained, the members of the committee were divided into review groups. She explained that each research application is routed by the coordinator to a specific group for review. In order to decide which group should review what file, the coordinator first checks for any COI between the reviewers and the application.⁶⁹⁰ The National Committee coordinator is a MOH employee and has access to the COI disclosed information based on the questionnaire provided by the member. The National Committee official interviewed stated that if there is a member in that group that works in the same hospital as the PI, the coordinator will transfer the file to another review group. Following initial COI screening, the coordinator then checks the context of the application and transfers the file based on the group members' expertise.⁶⁹¹

One interviewee suggested that in addition to the disclosure requirement based on the questionnaire, there is in fact another practical way to finding out relational associations with the applicant. She indicated that in the majority of the cases, one can tell from the applicant's last name being the same as the member's.⁶⁹² Having said that, another member of the National Committee interviewed suggested that in fact there is no good mechanism to discover whether people are dishonest. He gave an example in which a committee member was taking active part in the research review and later became startup investor for the product under review. He stated that at the time of the discussion, the other members of the committee had no way of knowing that this would happen. This interviewee, however, emphasized the non formal sources of information, suggesting that in Israel "everybody knows everybody" [Translated from Hebrew] and so the truth comes out eventually.⁶⁹³

Finally, the MOH officials discussed briefly the differences in the process for identifying government advisory committees' COI and COI in ad hoc expert advisors. They stated that all MOH National Committees and Central Committees upon their nomination are required to fill out a COI form. The committee members' potential COI based on the disclosed information was thoroughly reviewed by the MOH legal department. They indicated that for the various ad hoc

⁶⁹⁰ Interview *supra* note 435.

⁶⁹¹ *Id.*

⁶⁹² Interview with National Committee member, at the member's office (September 14, 2010).

⁶⁹³ *Id.*

experts used by the MOH for various scientific or ethical inputs the process is different. They explained that these experts are required to fill out a short COI form; however their disclosed information is not reviewed by anyone. When asked the reason for such differences, they stated that an important difference exists between obtaining an expert's opinion and functioning as a regular member of an advisory committee. As explained, obtaining an expert's opinion for specific input does not have the same weight as serving as a member in a long term advisory committee. Thus, the process for identifying COI should be also different.⁶⁹⁴

5.4.3 Implications of Committee Member COI

Helsinki committees – conflict avoidance and recusal As opposed to the inverse correlation between definition and consequences found in investigator's COI discussed in Chapter 4, in the case of ethics committee COI the correlation was direct. The broader the definition of COI found, the broader the actions taken to eliminate or mitigate it. A wide consensus was found among all the hospital officials interviewed as to what should be the consequences of COI at the ethics committee member's level. They all indicated a conflict avoidance process in which the ethics member-investigator recused him or her from the meeting prohibiting them from taking part in the discussion or decision of their own application. They all mentioned a similar process in which mostly the chair declares the member's COI circumstances at the beginning of the meeting, while the member's recusal is reflected in the committee's minutes. The same process will be taken if the chair is in COI. Per an interviewee from hospital 7, this process is very common.⁶⁹⁵

Under certain circumstances, a member-investigator may be brought in front of the committee to provide more information. As officials from hospitals 1 and 4 indicated, the dual member-investigator might be called to present his or her application to the committee or provide information as deemed necessary for further clarification to the full committee. These interviewees emphasized that this member-investigator, however, will not be allowed to

⁶⁹⁴ Interview *supra* note 313.

⁶⁹⁵ Interview with hospital 7 official *supra* note 459.

participate in the discussion or in the decision.⁶⁹⁶ They all strongly stated that the assumption is that the Helsinki committee is very appreciative and respectful to the integrity of its members.

As mentioned above, an interesting disagreement was found between interviewees from hospitals 2 and 4 with regard to whether ethics committee members who had supervisory authority over the PI or the study would be regarded as being in COI. While the interviewee from hospital 2 found these cases problematic in terms of COI risks⁶⁹⁷, the interviewee from hospital 4 did not.⁶⁹⁸ Despite their disagreement as to what constituted COI, the two however, agreed about that no further actions should be taken. Thus both agreed that the supervisory member will be allowed to participate and decide upon the research at hand. However, they both disagreed about the reasons why. The interviewee from hospital 2 found these situations an essential part of the given circumstances where the committee members are also researchers themselves.⁶⁹⁹ The interviewee from hospital 4, however, found it necessary for the member with a supervisory position to participate and decide. As he stated: “If the member of the committee is the chief physician in the department where the research will take place, then he could and should participate in the discussion as he or she will have valuable information to add in the discussion.”⁷⁰⁰ [Translated from Hebrew]

National Committee – disclosure and management The members of the National Committee interviewed described a similar process of conflict avoidance and explicit protocols indicative of those described by the hospital officials.⁷⁰¹ The MOH officials further emphasized that the reason for having to explicitly write the recusal in the committee’s minutes is for transparency reasons.⁷⁰² However, the scope of COI definition was notably broader than those acknowledged by the hospital officials. The member of the National Committee interviewed explained that if the research applications reviewed by the National Committee relates to one of the researchers in his department, he physically leaves the room for the entire time of the discussion and decision.

⁶⁹⁶ Interviews with hospitals 1 & 4 officials, in the offices of hospital 2 & 4 Israel (August 30th & September 7th 2010 respectively).

⁶⁹⁷ Interview *supra* note 436.

⁶⁹⁸ Interview *supra* note 466.

⁶⁹⁹ Interview *supra* note 436.

⁷⁰⁰ Interview *supra* note 466.

⁷⁰¹ Interviews *supra* note 312 & 435.

⁷⁰² Interview *supra* note 313.

He stated that: “It is so clear that no committee member should review and discuss research applications in which they have interest. This is ethics 101.”⁷⁰³ [Translated from Hebrew] He mentioned that there is no need for any formal regulatory requirement, as this is so obvious. The MOH official interviewed somewhat disagreed, stating that even though this is very trivial and obvious process, there is still a room for a clearly written policy about that.⁷⁰⁴

An interesting nuanced approach was found with regard to the situation where the committee member also works for the same hospital as the applicants. According to MOH official interviewed, this fact by itself does not disqualify this member from taking part in the discussion and decision making.⁷⁰⁵ However, the National Committee member interviewed would likely disagree. As indicated by the interviewee, the decision to send the trial application to a certain team within the committee is based on the fact that the members of that team do not work for the same hospital as the applicant.

5.5 Discussion and Analysis of Interview Findings

Review of interview data and the relevant COI regulatory mechanisms underscores a number of issues relating to the practical application of the COI concept in the biomedical research involving human subjects at the research reviewers’ level. All the hospital officials, members of the National Committee and the MOH officials interviewed expressed a strong conviction in the integrity of their committee members involved in the research review process. The interviewees described highly qualified professionals working to provide the utmost ethical and scientific opinions to promote the scientific progress and at the same time provide adequate protection to the trial participants’ rights. In terms of COI issues, the regulatory framework distinguishes between the different actors involved in the research review process. While the various government advisory committees are governed by specific COI disclosure and management requirements, the institutional ethics reviewers are left to develop their internal policy on any COI of its members. The hospital officials interviewed indicated a conflict avoidance policy for situations where the conflicted ethics member-PI recused him or herself from the discussion and decision-making process. Based on the MOH specific COI Guidance applicable for government

⁷⁰³ Interview *supra* note 312.

⁷⁰⁴ Interview *supra* note 692.

⁷⁰⁵ Interview *supra* note 177.

advisors and the interview data, the next sections will discuss issues relating to the implementation of the current governance framework and institutional policy in terms of roles, standards and responsibilities.

5.5.1 Government Research Advisors and the “Shared Pool Dilemma”

Science, medicine, and technology have made a rapid progress during the last two decades becoming more specialized and sophisticated fields. With such fast pace advances and complexity, governments are finding it hard to keep up with progress in the various areas they regulate. Thus, the MOH, much like other regulatory bodies worldwide⁷⁰⁶, is in need to obtain recommendations from outside experts for proposed research not covered under their expertise. Not only is the MOH in constant need for highly qualified experts, but industry is looking for them as well. These highly qualified and experienced experts in the field are frequently in demand to serve as consultants to industry, PIs for clinical trials seeking entrepreneurial opportunities in startup companies. These circumstances whereby a limited number of scientific experts are in high demand to both the government and industry are described by McComas et al. as the “shared pool dilemma”.⁷⁰⁷ This is especially true in Israel, a small country, where the “pool of experts” is smaller than other more populated countries.

This shared pool dilemma raises the tension between impartiality and competence. In the U.S., this tension was subject to ongoing efforts by the FDA to reduce its advisors’ COI in order to maintain the public confidence in the neutrality of the process.⁷⁰⁸ Similarly, in Israel the MOH COI Guidelines were aimed at regulating COI among the various government advisors in order to maintain the credibility of the process in the public’s eye. The current COI screening procedure for government advisors used by the MOH includes several steps such as financial disclosure, detailed questionnaire response, review by the committee coordinator and the MOH

⁷⁰⁶ The U.S. FDA has been using the services of several advisory panels for scientific recommendations for years. In order to offer this scientific input, the U.S. FDA uses hundreds of outside experts many of whom serve as members of FDA advisory committees. For more information see the FDA commissioned report by the Eastern Research Group, *Measuring Conflict of Interest and Expertise on FDA Advisory Committees 2007*, available at <http://www.fda.gov/oc/advisory/ERGCOIreport.pdf> (last visited Sept. 7, 2012).

⁷⁰⁷ McComas et al. “shared pool” dilemma is described to be based on the two assumptions: the first that there is a limited number of qualified experts exists; and the second that the existing potential or real COI of these experts will result in that member acting in a biased manner. See Katherine A. McComas, Leah Simone Tuite & Linda Ann Sherman, *Conflicted scientists: the “shared pool” dilemma of scientific advisory committees*, *Public Understand. Sci.* 14, 285–303 (2005).

⁷⁰⁸ *Id.*

legal department, and final approval. This COI screening procedure together with the shared pool dilemma may increase the challenges of the MOH seeking to recruit staff to their advisory committees. Such challenges were indicated by the Director-General of the MOH. As the Director-General stated, in view of the COI screening rules and the fact that many experts who meet the qualifications have ties with industry, it is very difficult to find expert advisors to serve on the National Committee.⁷⁰⁹ Considering all the possible self-interests driving the individual when making decisions, it is impossible to use a wide preventive instrument without undermining the selection of people who could carry out administrative roles.

As discussed by McComas et al. there are two possible scenarios when trying to staff government advisors.⁷¹⁰ The first is when the government is more eager to settle the need for expertise due to COI. This may entail circumstances where the non conflicted member lacks the specific knowledge and expertise regarding the subject matter. Considering the vital responsibilities these member-experts provide, such a scenario is problematic. In fact not only do these advisory committees provide the MOH with recommendations on specific trial applications, but they also provide key advice on general policy matters to the government. Having many stakeholders in these committees with a lack of particular knowledge can undermine the purpose of having these committees in the first place. Also, as indicated by an FDA commissioned report, such COI screening procedures would incur substantial additional burdens in terms of the cost and timelines of the advisory committee's operations.⁷¹¹ A possible solution would be to balance the non-expert scientists with a few conflicted experts who have no voting authority.⁷¹² In other words, incorporating ex officio advisors authorized to advise the members of the advisory committees. From the interview data, it appears that, in Israel, from time to time, the National Committee indeed uses the services of various experts for additional input regarding the subject matter.

The second scenario entails the circumstances where the advisor has the requisite expertise, but is often conflicted due to current or prior associations with the industry. This situation may

⁷⁰⁹ Interview *supra* note 521.

⁷¹⁰ See McComas *supra* note 707.

⁷¹¹ See the Eastern Research Group *supra* note 706.

⁷¹² See McComas et al. *supra* note 707.

undermine the public trust and confidence in the decision-making processes. At the same time, as discussed in Chapter 2, banning COI circumstances might cause more damage than benefit. Arguably, it is in the public interest to allow highly qualified professionals to take part in the research review process, and therefore, applying such a stringent COI rule might deter capable review from taking place. Thus, as Shamoo and Resnik argue this COI prohibition rule should be implemented cautiously.⁷¹³

In the U.S., the FDA regulations allow a financially conflicted member to participate in the decision-making if they are granted a waiver. Waivers are mostly given in situations where the need for expertise outweighs the risks of COI.⁷¹⁴ In Israel, the nomination process includes a similar process to that in the U.S., in circumstances where the MOH officials together with the Deputy Attorney General are convinced that there is importance to allow the conflicted expert to be part of the discussion or decision-making process, as well as when no other expert with the same expertise exists.⁷¹⁵ Furthermore, the COI Guidelines require disclosing the affiliation information to the members of the committee at the beginning of the meeting.⁷¹⁶

No doubt, these strategies are required to ensuring that government advisors are perceived as not influenced by industry interests and are constantly seen to be working in the best interest of the public. However, the abovementioned process and decision to allow conflicted expert to participate are not made public. In addition, the National Committee minutes are also confidential. Thus, one might argue that to maintain the public confidence in the administrative processes particularly in important issues of public health and safety, more transparency of the process is in order. Such transparency may entail making available the specific criteria for nominating the various government advisors, along with the specific decisions for providing waivers to a conflicted-advisor enabling them to participate in the advisory process. For more discussion please refer to Chapter 7.

5.5.2 The Disclosure Deficiency Problem

⁷¹³ See Shamoo & Resnik *supra* note 14.

⁷¹⁴ See the Eastern Research Group *supra* note 706.

⁷¹⁵ See COI Guidelines *supra* note 304 at §16.

⁷¹⁶ *Id.* at §18.

As discussed above, the MOH has undergone a retroactive process in which all of its current advisory committee members were required to fill out COI questionnaires based on the MOH COI Guidelines. On the face of it, the COI Guidelines provide a simple COI review and management process for all those who serve as advisors to the MOH. The regulatory COI process requires that the committee coordinator and the legal department within the MOH review the detailed data provided by the advisory committee members to determine what will be considered COI and how, if possible, it will be managed. However, the standards for making such COI judgments are unspecified. The MOH officials are left to fill in these standards gaps. The problem with trying to fill in the regulatory standards gaps can be found in the MOH official interview. In her interview the MOH official indicated that she is not sure how to interpret the disclosed information, as the line for COI is not clear.⁷¹⁷

The problem of how to interpret potential COI based on disclosed information is discussed by the literature with regard to trial participants. Thompson calls it “disclosure deficiency” in which trial subjects receiving disclosed COI information from the trial investigator may not know how to interpret it. Thompson argues that disclosed COI information by itself may increase the level of anxiety for the trial participants, causing more suspicion.⁷¹⁸ Such deficiency in disclosure can also be attributed to the administrative actors who are in charge of reviewing it and making policy decisions on how to respond to it. Daphne Barak-Erez argues that since the administrative agencies are in charge of balancing interests, it is important that the authorizing regulations will include a clear definition as to the goal of such a balancing task as well as the considerations guiding the acting agents.⁷¹⁹

Can an unspecified regulatory COI principle enable good research governance practices? The existing literature frames the need for clear rules and standards for COI policies from a governance perspective on the element of transparency and accountability. As discussed in Chapter 4, the U.S. IOM report offers criteria necessary to evaluate actual operation of current COI policies. In accordance with the U.S. IOM report, transparency is necessary when

⁷¹⁷ Interview *supra* note 177.

⁷¹⁸ See Thompson *supra* note 34 at 295-297.

⁷¹⁹ See Barak-Erez *supra* note 660 at 217.

administrating COI policies.⁷²⁰ The IOM report stated that the COI policies should be clearly written, along with the necessary explanation on how to implement them. The IOM report further stipulates that in order for the public to evaluate whether these policies are reasonable, they should be easily available to them.⁷²¹ The IOM report calls for clear formulation of well defined COI rules to support improved confidence in the medical profession.

To enable the implementation of good public governance, well-defined standards, norms and processes are essential. In addition, readily available arrangements to implement these policies are also required.⁷²² The IOM report determines that in order to strengthen COI policies and procedures, the research community should come together to develop clear policies and consensus standards.⁷²³ Thompson discusses the growing role of governments in regulating COI issues specifically in the area of medical practice and research. Thompson argues that such growing interest results from the failure of the medical community to adequately combat the problem, and also from the “...greater stake that society has in medical practice and research.”⁷²⁴ Thompson argues that regulating COI by the government has its advantages due to the fact that more people are involved in the process of defining and enforcing the rules with a strong notion of transparency. At the same time, Thompson explores the potential disadvantage in virtue of the difficulties of matching the defined rules to the variety of conflicts that may arise.⁷²⁵ Apparently, the current Israeli regime, in reflecting upon its stand on essential COI standards and processes for the government advisors, leaves the MOH officials and the public with some fundamental unresolved questions.

5.5.3 COI at the Helsinki Committee Level - No Regulatory COI Provision and Narrow Application

Contrary to government advisors, the current regulatory scheme does not regulate potential COI for members of the institutional ethics committees. The hospitals are left to manage the ethical issues associated with their research reviewer’s COI internally. As indicated by the interview

⁷²⁰ See the IOM report *supra* note 32 at 58.

⁷²¹ *Id.*

⁷²² See Hirtle *supra* note 524.

⁷²³ IOM report *supra* note 32 at 1-4.

⁷²⁴ Thompson *supra* note 34 at 295-297.

⁷²⁵ *Id.*

data, the hospitals interviewed apply a strict COI abstention policy, in which the ethics committee member serving as the trial investigator will be prohibited from taking part in the discussion, deliberation and voting. Such policy focuses entirely on the attempt to prevent bias of the ethical review of trial application resulting from the dual responsibility of research reviewer and investigator. Nevertheless, other areas of COI discussed in the literature, such as research reviewers' own entrepreneurial interests or affiliation with the trial sponsor are not consistently addressed.

There is no doubt that COI situations compromise or are perceived to compromise objectivity. Baring in mind the obligations of the ethics committee members safeguarding the wellbeing of the participants and protecting the validity of the research data, these other associations potentially undermining objectivity should be explicitly addressed. Applying such narrow interpretation of possible COI circumstances by the Israeli hospitals is questionable. Such narrow interpretation may raise concerns for the robustness and effectiveness of hospitals' oversight and diligence in protecting the wellbeing of their trial participants. These concerns for a variety of potential COI circumstances ascribed to the institutional research reviewers, along with the emerging entrepreneurial nature of contemporary biomedical research, require further review and assessment by the research community and the Israeli regulator.

As discussed in Chapter 7, the necessity of adopting a clear and comprehensive COI policy to address the possible COI of the institutional ethics committee members was discussed in the U.S. by the joint advisory committee of the AAMC and AAU.⁷²⁶ In their comprehensive 2008 report, the advisory committee recommended medical institutions compose clear COI policies to address the disclosure and management of such COI. The report recommended that the provisions for COI disclosure should include all financial interests by IRB members, similar to those required from the trial investigators. The report further recommended explicit provisions specifying the procedure of which these COI will be identified and evaluated with a strong recusal strategy. The U.S. IOM report also discussed the significant role of these COI policies stipulating that "Policies designed to reduce COIs and mitigate their impact provide an important

⁷²⁶ AAMC-AAU 2008 report *supra* note 234.

foundation for public confidence in medical professionals and institutions.”⁷²⁷ The U.S. IOM report further warns that should the medical institutions fail to strengthen their COI policies, more pressure to impose government regulations will be increased.⁷²⁸

5.6 Conclusion

Similar to other nations, the Israeli biomedical regime has promulgated regulations directed at the protection of the primary goals of clinical research by virtue of an independent review and oversight model. Based on the institutional-state review model, the responsibility for the evaluation and oversight of human subject research is mainly bestowed upon the institutional Helsinki Committee and/or the officials at the MOH. As part of the ethical or scientific evaluation, the MOH is assisted by various professional committees and/or experts providing additional input and recommendations.

The emerging entrepreneurial nature of contemporary biomedical research, and the associations between the research reviewers and sponsors, creates several COI issues which challenges the core design of safeguards. The pivotal concern centers on whether the increasing commercial sponsorship and the growing financial incentives for reviewers and/or their institutions may have or be perceived to have impact on the reviewers’ impartiality. The challenge for these research reviewers is finding ways to maintain their impartiality when implementing their primary protective goals, without impeding the progress and commercialization of new technologies.

Several concerns were raised about the research reviewers’ ability to perform their primary objectives both in the U.S. and Israel. Particularly in Israel, the State Comptroller reported serious ethical and procedural deficiencies with respect to several institutional Helsinki committees. Concerns rose as to whether this ethics review system is well-equipped to safeguard the primary goals of human research. As opposed to rich and reliable empirical research and scholarly material regarding the work of the ethics committees in the U.S., very little data exist on the processes, procedures and policies of the members of Israel’s institutional ethics committees and the government advisory committee - National Committee.

⁷²⁷ IOM report *supra* note 32 at 51.

⁷²⁸ *Id.* at 1-4.

In terms of COI issues, the regulatory framework distinguishes between the different actors involved in the research review process. While the various government advisory committees are governed by specific COI disclosure and management requirements, the institutional ethics reviewers are left to develop their internal policy on any COI of its members. Another regulatory mechanism directed at COI, is the requirement to include public participation within the decision-making processes.

All interviewees expressed confidence in the integrity of their committee members. Overall, interviewees agreed that the dual responsibility of investigator-ethics members causes concerns for COI and bias. A conflict avoidance policy is implemented where the reviewer-PI recuses him or herself from the discussion and decision-making process. Nevertheless, differences were found between institutional reviewers and government advisor reviewers with regard to the scope and definition of COI when other possible interests are involved. Contrary to the inverse correlation found in Chapter 4, the interview data reveal a direct correlation between the scope of the definition of COI and the measures taken to eliminate or manage it.

The review of the practical implementation of the COI at the research reviewers' level in Israel has served to underline a number of research governance practices issues. Issues discussed in this chapter were based on the interview information and government mechanisms and include the following main points: the "Shared Pool Dilemma" raising tension between impartiality and competence; the "disclosure deficiency" a problem focusing on the difficulty in interpreting disclosed COI information under the current provisions; and the lack of regulatory COI provision for the institutional actors and the seemingly narrow application of the hospital internal COI policies.

CHAPTER 6: Institutional Conflict of Interest

This thesis examines the governance, operations and practices of Israel's biomedical scheme safeguarding against the risks associated with COIs in biomedical research. In five sections, this chapter seeks to theorize the conceptual and practical nature, extent and consequences of COI ascribed to institutions conducting medical research involving human participants. Similar to Chapters 4 and 5, this chapter applies two levels of analysis: conceptual and practical. The conceptual analysis, discussed in section 6.1, explores information about the Israeli hospitals conducting clinical research, and continues to focus on the framework of the largely institutional paradigm for approval and monitoring of clinical trials conducted at their premises. It then delves into various worldwide studies suggesting institutions' entrepreneurial interests creating financial COI, thereby calling into question the current self-policing strategy. The main concern is that potential biases within institutional decision-making practices and processes will jeopardize the health of research subjects, research integrity, and public trust.

The practical analysis in sections 6.2 and 6.3 shows that, unlike investigators and government advisors, the regulatory scheme does not provide mechanisms to address institutional COI. In fact, in some respect the regulatory provisions might intensify these institutional conflicts. This section will conclude with an exploration of the law requiring medical institutions to disclose information regarding donations provided by the industry thereby providing more transparency. Then, the analysis of section 6.3 focuses on the data obtained from interviews conducted with hospital professionals and officials at the MOH, to discuss how the institutions and the MOH are dealing with COI at the institutional level. Despite the absence of regulatory provisions, the interview phase suggests that some hospitals were addressing these conflicts applicable to financial interests held at their institution. Nevertheless, wide inconsistency was found in the measures taken at hospitals to respond to institutional COI.

The critique of this chapter, discussed in section 6.4, centers on the practical analysis of the implementation approaches to institutional COI in Israel, showing how these approaches raise a number of research governance practices issues. The following are among the critiques advanced in this chapter: rather than restricting clinical trial approval mechanisms to scientific and ethical considerations, the current regulatory regime appears to ensure joint assessment of factors related

to ethics and profit; some hospitals lacked organizational barriers separating the responsibility for oversight of human participants' studies from the responsibility for institutional investment endeavors and technology transfer program; and government created hybridized research institutions with profound financial incentives call into question the current regulatory and organizational framework and infrastructure and its ability to deal with potential institutional COI. The last section 6.5 summarizes and concludes the main findings.

6.1 Conceptualizing COI at the Research Institution Level

As of 2008-2008, general hospitals in Israel conducted the vast majority of clinical trials in drugs or non drugs or medical device. The high percentage of trials conducted at the general hospitals were the reason to focus the interview phase for the purpose of this study on these institutions. The section to follow describes the institutional paradigm for the approval and oversight of clinical trial based on the regulatory provisions. Whereas the last section discusses the government's advancing privatization model and its encouragement of entrepreneurialism of biomedical research, and how it raises concerns for institutional COI by virtue of the institution's position in safeguarding the primary goals of research. Namely, the growing financial opportunities for the non-for-profit hospitals can arguably put at risk their legal and moral obligation to protect the trial participants, research objectivity and public trust.

6.1.1 The Israeli Medical Institutions – Profile

The Public Health Regulations govern only medical research conducted in hospitals.⁷²⁹ The regulatory framework is silent with respect to medical research conducted in other facilities, such as private labs, medical schools and Contract Research Organizations (CROs). Scant information is available about research conducted outside hospitals in Israel. On the face of it, one might argue that there is no medical research conducted outside of hospitals in Israel. However, based on interviews conducted with MOH official and an advisor to the MOH, it is clear that hospitals are not the only venues requiring oversight.⁷³⁰ The interviewees revealed that a small portion of trials are indeed conducted in universities and CROs. The interviewees further confirmed that these trials are not governed under the regulations and in practice there is no oversight or

⁷²⁹ The Public Health Regulations *supra* note 138.

⁷³⁰ Interview with a member of the National Ethics Committee & MOH official, at the officials' office, Israel (September 11th & 14th respectively).

monitoring by the government.⁷³¹ The clinical trials conducted outside of hospitals are beyond the scope of this dissertation.

Hospitals are defined broadly as: “all medical institutions... and every building used, or intended to be used, to accept people that suffer from disease, injury, physical or mental impairment, and that provide for women giving birth, in order to treat all with medical care...”⁷³² [Translated from Hebrew]. Every hospital has to be managed by a licensed physician⁷³³, and the government is authorized to oversee hospital licensure and grant approval to open a new hospital or department.⁷³⁴ Further, the Director-General of the MOH has a wide range of authorities to issue regulations and rules with regard to hospitals’ licensing, operations, management, registration, monitoring and oversight.⁷³⁵ Lastly, the number and distribution of hospitalization beds is also regulated by the state.⁷³⁶

There are many medical institutions operating in Israel. These institutions can be distinguished by their source of funding, scope of services and whether or not they are affiliated with academia, acting as teaching hospitals. Based on MOH data, as of 2010, there are a total of 42,119 hospital beds among the different general and specialized medical institutions.⁷³⁷ Despite the fact that Israel has several small specialized medical facilities, the vast majority of hospital beds, about ninety percent, are in general hospitals⁷³⁸ and chronic disease institutions.⁷³⁹ Government owned hospitals provide more than twenty-seven percent of the overall hospital

⁷³¹ The interviewee from the National Ethics Committee added: “Today, research conducted by the academia is reviewed by the university’s committee... They are not “legalized” and it is not clear under what authority they work.” *Id.*

⁷³² Public Health Ordinance, 5701-1940, last revised 5772-2011 SH No. 22901 p. 742 (Isr.). Any establishment of a new hospital or any change to existing hospitals requires the approval of the Director-General of the MOH. See §24A.

⁷³³ *Id.* at §26.

⁷³⁴ *Id.* at §25(a).

⁷³⁵ *Id.* at §33.

⁷³⁶ For more information about the Israeli health system, please see Bruce Rosen & Hadar Samuel, Israel: Health System Review: Health System in Transition, European Observatory on Health & Policy 11, 2, available at http://www.euro.who.int/__data/assets/pdf_file/0007/85435/E92608.pdf (last visit Sept. 7, 2012).

⁷³⁷ See the MOH report, Hospital Beds & Licensed Work-Stations (2010) (Isr.), available at http://www.old.health.gov.il/Download/pages/Beds_jan_2010.pdf (last visited Sept. 7, 2012).

⁷³⁸ For more information about hospital institutions in Israel see the MOH report, Hospital Institutions & Short-term Hospitalizations in Israel *supra* note 320.

⁷³⁹ These mainly include geriatric institutions and nursing homes.

beds.⁷⁴⁰ The private hospitals own about thirty-four percent of the hospital beds mostly in chronic disease institutions⁷⁴¹, and a further thirteen percent are owned by Clalit Health Services.⁷⁴² The remaining hospital beds are distributed in various non-for-profit entities, including religious organizations and the Women’s Zionist Organization of America Inc⁷⁴³. Most of the hospital beds, however, are distributed among a relatively small number of medical institutions. Namely, only twenty-five of the total fifty five medical institutions operating in Israel have more than 200 hospitalization beds.⁷⁴⁴ Of Israeli’s forty-five general hospitals, the government owned hospitals provide a great percentage of the hospital beds, about forty-six percent; Clalit Health Services is second with about thirty percent; while only about three percent are privately owned.⁷⁴⁵ Figure 6.1 below shows the distribution of hospital beds in general hospitals owned by various entities.

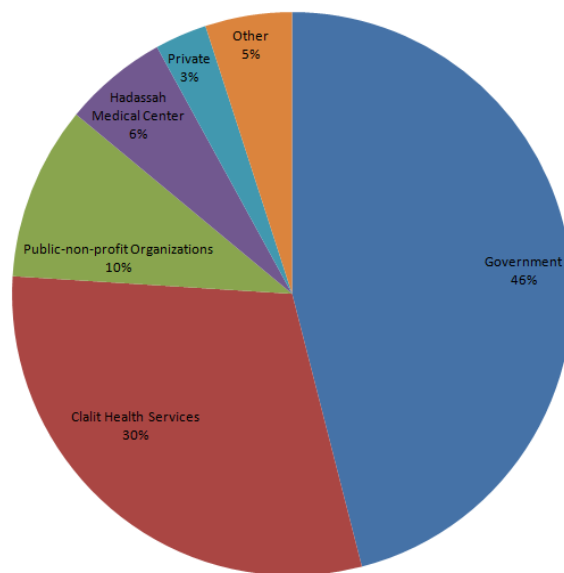


Figure 6.1: Distribution of Hospital Beds in General Hospitals 2009

Source: MOH data, Hospital Institutions and Short-term Hospitalizations in Israel 2009 report.

⁷⁴⁰ See the MOH 2010 report *supra* note 737.

⁷⁴¹ *Id.*

⁷⁴² As mentioned in previous chapters, Clalit Health Services is a non-profit health plan organization, similar to the U.S. HMOs, which operated its own network of hospitals and healthcare professionals.

⁷⁴³ The Women’s Zionist Organization of America Inc. owns the Hadassah Medical Center in Jerusalem.

⁷⁴⁴ See the MOH 2010 report *supra* note 737.

⁷⁴⁵ See the MOH 2009 report *supra* note 738.

The majority of the hospitals act as teaching hospitals with university affiliations⁷⁴⁶ operating training programs for medical students, interns and residents.⁷⁴⁷ The forty-five general hospitals are multi-district institutions located around the country. The general care bed-to-population ratio is higher in the center and northern regions of the country than in the periphery.⁷⁴⁸ The national health care expenditure has been relatively stable over the past two decades and, as of 2009, accounts for approximately 7.9 percent of Israel's GDP⁷⁴⁹, with hospitals and public clinics accounting for approximately 34.5 percent of the overall national health expenditure. Hospital revenue derives primarily from the sale of health services, with approximately 80 percent is generated from services provided to the members of the health plans on the basis of reimbursement rules regulated by the government.⁷⁵⁰

6.1.2 Hospitals Conducting Clinical Trials

Israel conducts 69.8 percent of all clinical trials in the Middle East and 3 percent of worldwide trials.⁷⁵¹ Israel has no national mandatory registry database specifying information regarding clinical trials conducted in the various institutions operating in its borders. Nevertheless, as of 2008, all clinical trials involving human participants should be registered in the U.S. National Institute of Health's registry of international clinical trials.⁷⁵² This requirement is necessary in order to comply with the 2007 International Committee of Medical Journal Editors' (ICMJE) guidelines, which state that a consideration for publication is registration in a public trials

⁷⁴⁶ There are four medical schools operating in Israel with each affiliated with certain general hospitals. They include: the Hebrew University Medical School; the Tel Aviv University Medical School; the Technion Medical School in Haifa and the Ben-Gurion University Medical School in Be'er Sheva.

⁷⁴⁷ The range and extent of the university affiliations varies among the hospitals. See Israel: Health System Review: Health System in Transition *supra* note 57.

⁷⁴⁸ The overall general care bed-to-population ratio is 2.1 per 1000 population. This ratio is higher in the center/northern region of the country, ranging from 1.5 in the southern region to 2.7 in the northern region. *Id.*

⁷⁴⁹ This is relatively low percentage compared to other member countries of the OECD, for example compared to France's 11.8 percent, the UK's 9.8 percent and the U.S.'s 17.4 percent. For more information see OECD Health Data Report (2011), available

http://www.oecd.org/document/16/0,3343,en_2649_34631_2085200_1_1_1_1,00.html (last visited Sept. 7, 2012).

⁷⁵⁰ For more information about the Israeli health system and stakeholders see Health System in Transition *supra* note 57.

⁷⁵¹ This is per the information available at the U.S. National Institute of Health registry's database. See *supra* note 239.

⁷⁵² See the Director General of the Ministry of Health notice No. 3/08 (Feb. 18th, 2008), available at http://www.health.gov.il/hozer/mk03_2008.pdf (last visited Sept. 7, 2012). As mentioned above, the Director General of the MOH has a wide authority to issue regulations and rules with regard to hospitals' operations, and these rules are binding to all medical institutions. See §33 of the Public Health Ordinance *supra* note 732.

registry database.⁷⁵³ However, it is difficult to extract information from the NIH database as to how many trials are conducted in each Israeli hospital in a given year, since this database does not allow a query of such information.⁷⁵⁴

In Israel, hospitals are required to provide the Pharmaceutical Administration of the MOH with an annual report regarding the ongoing and completed trials conducted on their premises.⁷⁵⁵ MOH data indicates that in 2009 the total number of ongoing clinical trial for drugs was 1,085 and for non-drugs or medical devices was 1,191.⁷⁵⁶ These data indicate that in 2008 there were a slightly higher number of trials 1,231 and 1,288 for drugs and non-drugs or medical devices respectively.⁷⁵⁷ Notably, clinical trials conducted outside of hospitals are not regulated, and thus are not required to report about its trial activities to the MOH. Thus, these data may only be partial of the complete number of drugs and non-medical device trials conducted in all the venues in Israel. These data show that in both 2008 and 2009, general hospitals conducted the vast majority of clinical trials. Namely, general hospitals conducted more than 87 percent of the clinical trials in drugs and more than 81 percent in non drugs and medical device trials in 2009. Similar percentages of trials were found in 2008.⁷⁵⁸ The high percentage of trials conducted at the general hospitals were the reason to focus the interview phase for the purpose of this study on them.

The aforementioned MOH data also show the distribution of clinical trials among the hospitals with different sources of funding. The data show that government owned hospitals and hospitals owned by the Clalit Health Services conducted the vast majority of all the drugs and non-drugs or medical device trials both in 2008 and 2009. Government owned hospitals conducted

⁷⁵³ For more detail about the ICMJE's guidelines, their website is available at: <http://www.icmje.org/> (last visited Sept. 7, 2012).

⁷⁵⁴ The data provided in the U.S. National Institute of Health registry's database include information regarding the types of trials, status of the trial and geographic location. See the U.S. National Institute of Health registry's database *supra* note 239.

⁷⁵⁵ See Guidelines for Clinical Trials *supra* note 35 at §15.4.

⁷⁵⁶ This information does not include data regarding ongoing trials for medical devices. The efforts to obtain the MOH data on clinical trials for medical devices with several emails requests were futile. See the MOH's Report, Number of New Clinical Trial Applications in Drugs and non Drugs/Medical Devices 2008-2009, (September 20th, 2010) (unpublished report) (on file with Author).

⁷⁵⁷ *Id.*

⁷⁵⁸ In 2008, the general hospitals conducted about 88 percent of the drugs trials and about 86 percent of the non-drugs/medical devices trials. *Id.*

approximately 50 percent and 47 percent of drugs and non-drugs or medical devices trials respectively in 2009. At the same time, the Clalit Health Services conducted about 34 percent and 34 percent of drugs and non-drugs or medical devices trials respectively in 2009. Together, the government owned and Clalit owned hospitals conducted more than 84 percent of all drug trials and more than 80 percent of non-drugs or medical devices trials in 2009. Figure 6.2 below shows the distribution of the clinical drug trials in hospitals owned by various entities in 2008 and 2009.

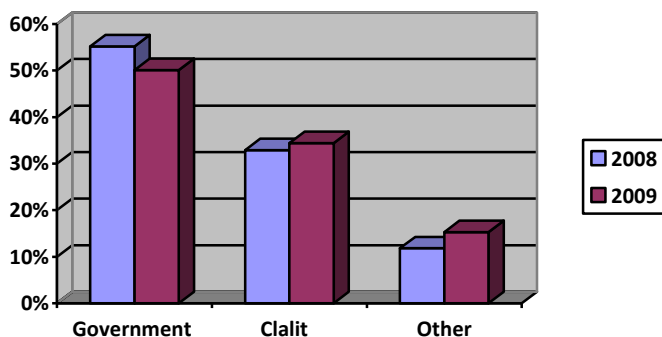


Figure 6.2: Distribution of Clinical Drug Trials in Hospitals 2008 and 2009⁷⁵⁹

These data can also show direct correlation between the size of the hospital, the number of hospital beds, and the number of trials. The data show that the bigger the hospital, the higher the number of hospital beds; and the broader the range of services and functional units, the higher the number of trials conducted.⁷⁶⁰ The MOH official interviewed affirms these findings, stating that the biomedical companies prefer to work with the big hospitals.⁷⁶¹ Namely, the three general hospitals with the highest number of hospital beds (each with more than 1,000 beds) -- The Chaim Seba Medical Center; the Tel Aviv Sourasky Medical Center; and the Rabin Medical Center -- are the three hospitals with the highest number of drug trials conducted as of 2009. As discussed in the methodology section of Chapter 1, these hospitals were part of the seven purposive sampling chosen for this research.

⁷⁵⁹ The Author analysis of the Ministry of Health data, Number of New Clinical Trial Applications in Drugs and non-Drugs or Medical Devices 2008 and 2009 reports (unpublished report) (on file with Author).

⁷⁶⁰ *Id.*

⁷⁶¹ Interview with MOH official *supra* note 185.

Also, the fact that the general hospitals owned by both Clalit and the government conduct the vast majority of the clinical studies in the country further connects the purposive hospital sampling chosen for the interview phase of this study. As discussed in the methodology section, of the seven hospitals chosen for the purpose of this study, six are either government or Clalit owned, and one is owned by another non-profit organization. Together the seven hospitals conduct the vast majority of the trials and they also contain the highest number of hospital beds in Israel. In order to obtain information regarding the processes and practices of the current system, the goal of the interview stage was to interview hospital officials conducting most of the clinical trials in Israel.

In sum, the Israeli biomedical regulatory regime regulates only medical research conducted in hospitals. Hospitals are defined broadly, and the government regulates their licensing, operations, and management. The majority of hospitals act as teaching hospitals with university affiliations. Despite having several small specialized medical facilities, the vast majority of hospital beds are located in general hospitals and chronic disease institutions. Of Israeli's forty-five general hospitals, the government owned hospitals and hospitals owned by Clalit Health Services provide the vast majority of the hospital beds. As of 2008 and 2009, the general hospitals owned by the state and Clalit Health Services conducted the vast majority of clinical trials in the country. Indicated by MOH data, direct correlation was found between the size of the hospital, its number of hospital beds, and the number of trials. Lastly, the MOH data do not contain information regarding trials conducted in other venues as these venues are not regulated by the government. Further inquiry, although not covered in this study, is nevertheless imperative as to the scope and nature of these studies.

6.1.3 Institutional Paradigm with Limited Government Oversight

Generally, the Israeli biomedical regulatory scheme requires safeguarding human participants' well-being and the scientific validity of all research with human subjects.⁷⁶² The Declaration of Helsinki, explicitly adopted by the Guidelines for Clinical Trials, further recognizes the right to

⁷⁶² Guidelines for Clinical Trials *supra* note 35 at the General section.

protect the “...life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.”⁷⁶³

The Israeli regulatory regime has implemented these rights through various requirements, including provisions for the informed consent process,⁷⁶⁴ risk-benefit analyses⁷⁶⁵ and eligibility criteria for participant selection.⁷⁶⁶ The role of scientific and ethical scrutiny of all studies conducted in hospitals was put into the hands of two key stakeholders: the medical institution - through its ethics committee and the director of the institution - and the MOH. As discussed in detail in Chapter 5, all clinical studies on human subjects have to be approved by: (1) the medical institution’s governing Helsinki Committee with the approval of the institution’s director, and/or (2) the Director General of the MOH or its designees.⁷⁶⁷

Furthermore, post-approval monitoring mechanism exists at three levels of supervision:

- 1) By the Helsinki committee to supervise approved trials based on annually or adverse events reports received from investigators.⁷⁶⁸
- 2) By the hospitals audit panel to review and monitor ongoing clinical trials approved at the institution.⁷⁶⁹
- 3) By the MOH oversight through on-site inspections.⁷⁷⁰

These institutional actors along with the MOH play a significant role in evaluating any potential or apparent scientific or ethical violations throughout the duration of the trial, acting as “gatekeepers”⁷⁷¹ to safeguard and promote the primary goals of clinical research. In essence, the

⁷⁶³ See the Declaration of Helsinki *supra* note 33 at §11.

⁷⁶⁴ See Guidelines for Clinical Trials *supra* note 35 at §3.

⁷⁶⁵ According to §1.3(a), the Ethics Committee will not approve a trial on human unless: “...the expected benefits to the trial participant and to society justify the risk and the discomfort to the trial participant.” As well as subsection (e) “The foreseeable risks to the trial participant are minimized to the greatest extent possible by the use of appropriate research methods, and, where possible, the use of procedures already performed on human subjects or tested in animals.” *Id.*

⁷⁶⁶ *Id.* at §1.3 (f).

⁷⁶⁷ See Public Health Regulations *supra* note 138 at §2 - 4.

⁷⁶⁸ See Guidelines for Clinical Trials *supra* note 35 at §18.1.

⁷⁶⁹ *Id.* at §18.2.

⁷⁷⁰ *Id.* at §18.3.

⁷⁷¹ Schatz *supra* note 229.

regulatory regime formed a “partnership”⁷⁷² between the MOH and the hospitals to determine scientific and ethical priorities. In effect the institutional actors - the Helsinki committees, the director of the institution and the audit panels - bear the primary responsibility for the approval and/or oversight of biomedical research with human participants. Giving the role of approval and oversight to the various institutional actors allows these institutions to maintain considerable autonomy. The question arises as to whether such institutional autonomy is appropriate given the fact that biomedical research had changed becoming a competitive and entrepreneurial enterprise. In other words, with the emerging entrepreneurialism of contemporary biomedical research, the current design of safeguards and the designation of stakeholders in charge of enforcing regulations are now being called into question.⁷⁷³

6.1.4 “Hybridized” Public Institutions and Institutional COI

In general, Israel has been undergoing a profound transformation of privatization.⁷⁷⁴ As discussed in detail in Chapter 2, the Israeli government has adopted and implemented a “free market” economic model aimed at reducing the government’s expenditure on social services, such as education and health,⁷⁷⁵ and deregulating publicly held institutions.⁷⁷⁶ According to Barak-Erez, such transformation is attributed to strong U.S. political and cultural influences on the Israeli public which made the private-oriented economy model more appealing.⁷⁷⁷

As part of the ongoing privatization aimed to provide government owned hospitals even more autonomy and control, the government has allowed some of these hospitals to establish independent trust funds within their facilities.⁷⁷⁸ Through trust funds, these hospitals as well as

⁷⁷² Riley discusses similar partnership created by the federal regulations in the U.S. Essentially, the federal regulations created such partnership between the federal government through the NIH agency and the academic medical community within its role to approve and oversee medical research. See Margaret Foster Riley, *The Future of Regulation: Federal Funding and the Institutional Evolution of Federal Regulation of Biomedical Research*, *Harv. L. & Pol’y Rev.* 265 (2011).

⁷⁷³ *Id.*

⁷⁷⁴ Israel’s economic model has been going a profound transitioning from government centralized system to privatization. This economic transitioning mirrors the political transformation from a socialist ideology at the beginning of statehood to free market ideology. See Barak-Erez *supra* note 102.

⁷⁷⁵ See Flic *supra* note 144.

⁷⁷⁶ See Flic *supra* note 145.

⁷⁷⁷ See Daphne Barak-Erez *supra* note 659 at 206.

⁷⁷⁸ These health trust funds have been funded primarily through the sale of after-hours healthcare services to the health funds and for administrating clinical research on behalf of the industry. These hospitals were interested in establishing these funds in view of the fact that it provided these hospitals with greater autonomy in spending this

other public not-for-profit hospitals have begun operating and implementing business-like organizational schemes to maximize profits or simply to remain solvent.⁷⁷⁹ These hospitals have introduced several private, patient-funded services to generate income.⁷⁸⁰ As part of the effort to generate additional revenues, public hospitals have also collaborated with the biomedical industry to generate fees for administering clinical trials on their behalf. Revenues generated by public hospitals in Israel from industry initiated clinical trials have contributed to the hospitals' operations including the ability to obtain advanced medical equipment.⁷⁸¹ In fact, during 2010, public not-for-profit hospitals generated⁷⁸² 282 million NIS from administering clinical trials for the industry.⁷⁸³

In addition to furthering privatization, the Israeli government began assessing and adjusting legal and organizational frameworks in several areas to enable the potential commercialization of intellectual property generated with public research funds.⁷⁸⁴ The goal was to adopt new policies allowing certain performing research institutions, including government-owned hospitals, to retain ownership of the intellectual property rights arising from publicly funded research. An inter-ministerial⁷⁸⁵ steering committee was formed in 2003 to adjust the legal framework to facilitate the commercializing of intellectual property generated at government owned hospitals. This committee found that enabling government-owned institutions to hold the intellectual property rights to their inventions, would help generate social and economic benefits from the

money as oppose to money received from the government's budget. These trust funds have now grown to the extent that now they account for over 10 percent of the activity of the government hospitals. See Israel: Health System Review: Health System in Transition *supra* note 57.

⁷⁷⁹ See Flic *supra* note 144.

⁷⁸⁰ Such services allow patients to choose their specific surgeon or treating physicians, and to shorten the time for the operation. Such service requires an additional payment on top of the basic cap paid for hospital services. Israel Medical Association supports in providing private hospitals services within the all the public hospitals in Israel. They maintain that such private hospital services will better utilize the facilities and allow the hospitals to have revenue generating mechanism. See Horev & Babad *supra* note 41.

⁷⁸¹ See Hochman et al. *supra* note 149.

⁷⁸² Money generated from clinical trials by the industry is streamed to the hospital research funds.

⁷⁸³ See the Marker report *supra* note 9.

⁷⁸⁴ This mirrors the worldwide trends in intellectual policies instituted by many OECD countries, transferring the ownership of the intellectual property rights to the performing institutions. For more information about international trends in intellectual property policies, see OECD, Turning Science into Business: Patenting & Licensing at Public Research Organizations, Paris, France, Organization for Economic Co-Operation and Development (2003).

⁷⁸⁵ This committee included professionals from various government offices, such as representatives from the Ministry of Justice, Ministry of Finance and the Civil Service Commission. See the report of the Inter-ministerial Steering Committee to Regularization of the Intellectual Property in the Government Offices (Dec. 2005) available at <http://www.ag.mof.gov.il/NR/rdonlyres/> (Isr.) (last visited Sept. 7, 2012).

research conducted at the institution.⁷⁸⁶ According to the OECD, many of its member countries have become more aware of the value of their intellectual property, realizing that inserting the production of publicly funded research into the public domain is not sufficient to generate such important social and economic benefits.⁷⁸⁷ The director of Hospital 5 interviewed explained: “The government owned hospitals recently understood that they should not lose their intellectual property rights.”⁷⁸⁸

6.1.5 Institutional COI and Intellectual Rights

Currently any intellectual property rights to inventions discovered at the government-owned hospitals are owned by the government, although the hospital has the right to work on its behalf.⁷⁸⁹ As discussed in detail in Chapter 2, the MOH together with the Ministry of Finance are working on adjusting the regulatory framework to formally grant government hospitals a portion of the patent rights of new discoveries made possible by public funding.⁷⁹⁰ The government acknowledged that enhancing the commercialization of Israeli biotechnology products had become a national priority.⁷⁹¹ From an interview conducted with the Director-General of the MOH, this initiative is currently in its draft-revision phase.⁷⁹² The goal is to incentivize government hospitals to commercialize their scientific discoveries by allowing them the opportunity to generate patent related income.

Indeed based on the government initiatives and approaches, many not-for-profit hospitals, including government-owned, responded to the new policy by adopting for profit management models to facilitate technology transfer from their research facilities to the commercial marketplace. Based on the current government initiative, public not-for-profit hospitals will be entitled to receive royalties from the sale or license of the technologies created at their

⁷⁸⁶ The inter-ministerial report maintained that granting the government owned hospitals the rights to the intellectual property generated with public funds will lead to better disseminate the scientific-medical knowledge, help generate more income for future research, and also benefits the hospitals reputation. See *Id.*

⁷⁸⁷ See the OECD 2003 report *supra* note 784.

⁷⁸⁸ Interview with hospital 5 official *supra* note 505.

⁷⁸⁹ See the Government’s decision No. 4150 (Aug. 9th, 2005) available at <http://www.pm.gov.il/PMO/Archive/Decisions/2005/08/des4150.htm> (last visited Sept. 7, 2012).

⁷⁹⁰ For the last few years hospitals have been lobbying for regulatory changes in order to seek ways to increase their revenues in view of the constant health funds pressure to lower their services rates. See Horev & Babad *supra* note 41.

⁷⁹¹ *Id.*

⁷⁹² Interview with the Director-General of the MOH *supra* note 521.

institutions by their employee-researchers.⁷⁹³ Within the sampled hospitals, four out of seven have R&D departments and trust fund corporations within their facilities who are in charge of enforcing and protecting the hospital's intellectual rights. All of the hospital officials interviewed indicated that their institution hold the patent rights to its discoveries, although the extent of these rights varies.

The government policy goals echo the objectives of the U.S. Bayh-Dole Act from 1980 (35 U.S.C. §200-212). As discussed in Chapter 2, the Bayh-Dole Act was designed to incentivize public universities to commercialize their discoveries.⁷⁹⁴ Briefly, this Act allows hospitals to retain the patent rights for inventions formed and funded in government-sponsored research, and hence allows the institutions to profit from its commercialization.⁷⁹⁵ As a result, U.S. academic institutions have increased technology transfer and thrived on their ties with industry.⁷⁹⁶ A survey reported that about two thirds of U.S. academic medical centers hold equity rights in companies that fund research within the same institution.⁷⁹⁷ Most academic institutions have technology transfer offices facilitating revenues from intellectual property.⁷⁹⁸ Universities in the U.S., for example, generated much more income from patent licensing in 2000 (997 million dollars than in 1991 121 million dollars).⁷⁹⁹ The overall related financial benefits from licensing provisions with industry are estimated to generate close to 2 billion USD annually for U.S. academic medical centers.⁸⁰⁰ In general, economic literature in the U.S. supports technology transfer policies, arguing that such policies are effective tools for promoting national growth.⁸⁰¹ However, many critics argue that this act has also contributed to the erosion of the public's trust

⁷⁹³ For more information about the intellectual property financial opportunities, see Du Val *supra* note 11.

⁷⁹⁴ The 1980s – 1990s area reflected the critical change in public policy in the U.S. pertaining to technology transfer and competitiveness. See Bozeman *supra* note 154.

⁷⁹⁵ See Liang & Mackey *supra* note 595.

⁷⁹⁶ Studies show that the growth of the technology transfer framework in the U.S. corresponds to the biotechnology growth as well as to the growth in the industry's investment in health research. See Neetika Prabhakar Cox, Christopher Heaney & Robert M. Cook-Deegan, Conflicts Between Commercial and Scientific Roles in Academic Health Research, In *Trust & Integrity in Biomedical Research: The Case of Financial Conflicts of Interest* 41 (Thomas H. Murray & Josephine Johnston eds.), (Johns Hopkins 2010).

⁷⁹⁷ Bekelman et al. *supra* note 16.

⁷⁹⁸ In the U.S. for example, the Bayh-Dole Act 1980, goal was to encourage commercialization of academic discoveries as the Act allows researchers and research institutions the option under certain circumstances to retain the IP rights of their discoveries for government funded research. This act was codified as 35 U.S.C. §200-212.

⁷⁹⁹ See Blumenthal *supra* note 18.

⁸⁰⁰ See Liang & Mackey *supra* note 595.

⁸⁰¹ Bozeman & Sarewitz *supra* note 156.

in the academic enterprise, as universities and individual investigators are now perceived as profit-driven entities.⁸⁰²

The Israeli government's commercialization incentives policy may enable entrepreneurship for hospitals and their scientists taking an active role in the commercialization of their discoveries. It might also serve to produce significant and innovative scientific progress and health developments, as well as improve the quality of their research. At the same time, the emphasis on active intellectual property stances will also help to build closer collaboration between government hospitals and industry, promoting a competitive and entrepreneurial research enterprise. Currently, it is difficult to assess how much clinical research in Israel is funded by industry as there are no published data. Partial data are published regarding the amount of funding provided by industry for research in state-owned hospitals and hospitals owned by the Clalit Health Services. Based on these data, it is apparent that industry support for clinical trials has been more or less increasing in the last few years.⁸⁰³ MOH data reveal that in these hospitals in the years of 2009 and 2010 the private biomedical sector invested approximately eighty million dollars⁸⁰⁴ in clinical trials in Israel. Interview data indicated that the vast majority (60-80 percent) of drug trials in Israel are sponsored by commercial industry, whereas for non-drug trials (such as medical devices) only about 10 percent.⁸⁰⁵

Facilitating technology transfer mechanisms to generate revenues along with strong collaboration with the industry, introduces issues of competitive commercial interests into the public arena, which can arguably bring to light the most critical tension between private and public interests. While the public interest paradigm focuses on maintaining open and free access to intellectual discoveries, private interests seek to control and restrict access to information in order to maximize profit.⁸⁰⁶ Blurring the traditional distinction between public and private institutions,

⁸⁰² See Molinoff *supra* note 140 at 282-283.

⁸⁰³ The MOH data indicates that during the years 2006 – 2009, the industry's investment in clinical trials conducted at the government owned hospitals and those owned by Clalit rose from approximately NIS 202 million in 2006 to NIS 291 million in 2009. See the MOH's Committee for Contracts with Commercial Companies Report, Commercial Companies Investments during the years 2006-2009 in Clinical Trials, (no date unpublished report) (on file with Author).

⁸⁰⁴ See Roni Linder-Gantz *supra* note 9. Notably, other publicly and privately hospitals, are not required to provide data regarding research funding to the MOH.

⁸⁰⁵ Interview with MOH officials *supra* note 313.

⁸⁰⁶ See Bouchard *supra* note 15.

Krimsky calls this new class of entrepreneurial not-for-profit institutions “hybridized institutions”.⁸⁰⁷

The Director-General of the MOH addressed the difficulty in reconciling the MOH initiative with potential institutional COI. As he stated: “The question of institutional COI and IP rights for hospitals owned by the state is a policy question. How do we regard public institutions dependent on state budgets that now penetrate the business world? ... The fiercely global competitive business scheme is part of our reality. The big question is how do we reconcile this reality to public sector ideology? We can compromise, to allow the public institutions to slightly penetrate the business sector by giving them the option to offer certain private medical services... or allow them to retain the IP rights, etc. As long as they continue to meet public goals, they can still make some profit from the public. This situation is the lesser of two evils.”⁸⁰⁸ [Translated from Hebrew]

These entrepreneurial hybridized hospitals raise concerns for COI by virtue of their position in safeguarding the primary goals of research. Namely, the growing financial opportunities for these non-for-profit hospitals can arguably put at risk their legal and moral obligation to protect the trial participants and research objectivity.⁸⁰⁹ The scholarship sees these concerns as institutional COI. The U.S. IOM report defines Institutional COI as when the “...institution’s own financial interests or those of its senior officials pose risks of undue influence on decisions involving the institution’s primary interests.”⁸¹⁰ The institution’s senior officials, such as the director, management personnel and department heads, are responsible to make decisions in the best interests of the institution. A possible conflict may occur, for example, where the research conducted by the institution may affect the value of the institution’s patents or its equity holding in a pharmaceutical company. The concern is whether the institution’s financial interests could

⁸⁰⁷ Krimsky discusses the contemporary fusion of the business and academic sectors creating “blended institutions” which causes concerns for COI. See Sheldon Krimsky, *Academic Integrity: Combating the Funding Effect in Science: What’s Beyond Transparency?* 21 *Stan. L. & Pol’y Rev* 81 (2010).

⁸⁰⁸ Interview *supra* note 521.

⁸⁰⁹ Other scholars expressed their ethical concern regarding the equitable distribution of the significant profits made from public funding. Per Bouchard, when the substantial profits were generated from public contribution, the regulatory system needs to ensure equitable sharing to the public to avoid exploitation. See Bouchard *supra* note 15.

⁸¹⁰ See the IOM report *supra* note 32 at 218.

create biases within the institutional decision-making practices and processes ultimately jeopardizing the health of research subjects and research integrity.⁸¹¹

Potentially, authorized institutional decision makers may feel pressure to approve or encourage research which may not meet scientific or ethical standards. The concern is that institutions will take on scientifically or ethically questionable research because they can profit from doing so. Additionally, senior officials may favor distribution of institutional resources, including funding, equipment or personnel to industry funded research or potentially commercially marketable projects.⁸¹²

The IOM report acknowledges the risks of institutional COI to be as serious as those created by individual COI.⁸¹³ As discussed in Chapter 2, a serious debate exists in the literature as to whether there is clear evidence showing that COI has directly resulted in serious outcomes for patients. According to Blumenthal⁸¹⁴, some cases have created the suspicion or the appearance that it did.⁸¹⁵ Regardless of the debate over the risks posed to trial participants, the institutional COI calls into question the motives and decisions made by these hybridized hospitals, and risks undermining the public trust in research.⁸¹⁶ The IOM report is concerned that without responding to institutional COI, the findings of research associated with such institutional COI may be perceived as questionable despite the fact that there may have been no COI impact at all.⁸¹⁷ David Korn sees the question as being how, in the presence of institutional financial COI, the public can be confident that those who are in charge of implementing a trial are not biased and can still be trusted?⁸¹⁸

In sum, as part of the ongoing privatization policy, the government encourages its owned hospitals as well as other public non-for-profit hospitals to operate and implement a for-profit

⁸¹¹ Gatter *supra* note 27.

⁸¹² Du Val alleges that fee obtained from the industry for administrating clinical trials on their behalf may skew the institution's research policy by virtue of allocating the resources on studies with commercial potential while avoiding other social valuable research possibilities. See DuVal *supra* note 11.

⁸¹³ See the IOM report *supra* note 32 at 216

⁸¹⁴ See Blumenthal *supra* note 214.

⁸¹⁵ Often mentioned by the literature is the classic Gelsinger case discussed in *supra* note 215.

⁸¹⁶ See Liang & Mackey *supra* note 595.

⁸¹⁷ See the IOM report *supra* note 32 at 216-217.

⁸¹⁸ See Korn *supra* note 397.

management model to maximize revenues, thereby creating “hybridized institutions”. In Israel, studies shows that there is increasingly available support from the private sector as well as close collaboration between for-profit corporations and research institutions. Furthermore, not-for-profit hospitals through their trust funds have been increasingly pursuing profit and commercialization avenues along with their research and development work. These entrepreneurial hybridized hospitals raise concerns for institutional COI by virtue of their position in safeguarding the primary goals of research. The main concern is that potential biases within the institutional decision-making practices and processes will jeopardize the health of research subjects, research integrity, and public trust.

6.2 Managing Institutional COI under the Israeli Regime

6.2.1 Lack of Regulatory Response to Institutional COI

Unlike COI at the individual-researcher or government advisor level, the Israeli biomedical regulatory scheme does not address the risks of institutional COI. Moreover, as discussed in Chapter 5, the regulatory framework also does not address COI at the ethics committee level since they do not require such committee members to disclose possible COI. There is no published scholarly material or studies conducted on the topic in Israel. In fact, even in the U.S. the vast majority of the attention by the government, the media or the public has been on COI at the individual-investigator level.⁸¹⁹ The director interviewed at hospital 5, while aware of the absence of any regulatory guidance or hospital policy, explained that institutional COI is a new concept which should be addressed in Israel. He indicated that this new concept needs further review especially in view of the MOH policy initiative to enable government institutions to hold some portion of the patent rights in discoveries funded by the public. In his opinion, such a policy may intensify the potential institutional COI among the government-owned hospitals conducting clinical research.⁸²⁰

Not only does the regulatory scheme not address institutional COI, but in some respects the Public Health Regulations themselves might be intensifying these institutional COI. As mentioned in Chapter 5, each institution’s ethics committee – Helsinki committee – it required to

⁸¹⁹ See the IOM report *supra* note 32 at 219.

⁸²⁰ Interview *supra* note 505.

include a representative affiliated with the institution's management.⁸²¹ In fact the Public Health Regulations explicitly stipulate that in order to obtain a legal quorum, the institution's management representative has to be present in the Helsinki committee's meeting.⁸²² Such provision makes certain that the institution's interests are a significant part of the ethical evaluation and decision-making processes involved in the approval and oversight of clinical trials. In stark contrast, in the U.S., both the FDA and the DHHS regulations explicitly require that each of the institutional review boards (IRB equivalent to the Israeli Helsinki committee) include at least one member *not affiliated* with the institution.⁸²³ The goal is that ethical and scientific decisions be separated from the related financial and institutional decisions.

The reason for including a management representative on the ethics committee might be found in the historical development of biomedical regulations. As discussed in Chapters 2 and 5, before 1980, Israeli approval and oversight of clinical research was a state run review model where all research applications were subject to the Pharmaceutical Administration's approval at the MOH.⁸²⁴ In view of the growing number of trial applications, in 1980, the Director General of the MOH created the capacity for decentralization by allowing medical institutions and their individual Helsinki committees to conduct institutional review of applications.⁸²⁵ The Public Health Regulations and the Guidelines for Clinical trials specify that many responsibilities will fall to the director of the institution including providing the final approval in writing for the trial application once the ethics committee has given its approval.⁸²⁶ The Guidelines for Clinical trials explicitly stipulate that it is "the authority of the Director of a medical institution to approve clinical trials delegated by the Director General of the Ministry of Health. This authority is conditional on full compliance with the requirements set forth in the Guidelines and Regulations, and may be revoked in the event of failure to comply with these requirements."⁸²⁷

⁸²¹ See Public Health Regulations *supra* note 138 at §1 second Appendix.

⁸²² *Id.*

⁸²³ Such unaffiliated member is selected to represent the subject population of the specific interests tested for that trial. See 21 CFR 56.107 and 45CFR part 46.107 respectively.

⁸²⁴ See Bilig *supra* note 136.

⁸²⁵ For detailed information regarding the Israeli biomedical research approval and oversight rules and processes, please see chapter 3.

⁸²⁶ See Public Health Regulations *supra* note 138 at § 2(a).

⁸²⁷ The Guidelines for Clinical Trials *supra* note 35 at §5.

Per the MOH official interviewed, the biomedical regulatory regime imposes personal responsibility upon the hospital director should anything happens in the trial conducted at his or her institution.⁸²⁸ The MOH official interviewed further explained that in view of such responsibility, the hospital director wants his confidant (management personnel) to take part in the approval process to represent the director's interests. The interviewee clarified that the management representative in the ethics committees is responsible to protect the ethical interests of the institution, and by no means to maximize the hospital commercial interests.⁸²⁹

This explanation raises some interesting questions and is problematic at best. First, if the management representative, as the director's confidant, approves the trial application, the requirement for the additional approval by the director is redundant. Secondly, some of the hospital officials interviewed argue that the reason for having the management representative within the ethics committee is to protect the financial interests of institution, especially its intellectual rights.

6.2.2 Indirectly Addressing Institutional COI – the Donation Disclosure Law

As discussed in Chapter 2, the strong ties between the biomedical industry, public hospitals and public physicians have come under Israeli legislature's scrutiny. In 2008 the legislature enacted a rigorous statutory disclosure and reporting provision which was later revised in 2010.⁸³⁰ This statutory provision imposes reporting requirements of any monetary donation or donation of worth made by drug and medical device companies operating in Israel to a variety of recipients.⁸³¹ The list of recipients is very broad and includes not-for-profit medical institutions, patients' advocacy groups, universities and physicians. This statutory provision has two central goals: 1) provide the MOH with an effective tool to manage COI in areas of health⁸³²; 2) allow more transparency in the way healthcare stakeholders are rewarded for their role in the medical

⁸²⁸ Interview *supra* note 177.

⁸²⁹ *Id.*

⁸³⁰ *Supra* note 188.

⁸³¹ This reporting mechanism was initiated by the Ministry of Finance in the effort to oversee the cost of prescription drugs and medical device in the national healthcare budget. According to the introduction section of the law, of the 30 billion NIS of the annual national healthcare spending 6 billion NIS is spent on drugs and medical devices. See the introduction to §29 of chapter 7 of the Arrangement Law 2010 available at <http://www.shituf.gov.il/discussion/285> (last visited Sept. 7, 2012).

⁸³² See Levy *supra* note 189.

products development process.⁸³³ By enacting this provision, the legislature explicitly addressed the potential threat to judgment objectivity that can come with industry involvement and thus demanded more transparency.

This statutory provision focuses on the appropriateness of donations paid to those who can influence either the purchase or distribution of pharmaceuticals, medical devices, and other goods and services, or those who sell and distribute those goods and services. Notably, the disclosure is imposed on both the donor and the recipient.⁸³⁴ Disclosures are to be forwarded to the MOH and will be posted on its website. There is no doubt that this reporting requirement will increase transparency, allowing both the public and the MOH access to essential information related to potential COI. Since this reporting applies to both researchers and institutions, it will enable scientists, policymakers and even the public to identify the prevalence of COI both at the individual and institutional levels. Nevertheless, such a disclosure requirement is incomplete as the provisions only require the reporting of donations and not any other related fees or sale related practices. In addition, this disclosure provision does not require public hospitals to disclose information regarding the institution's own entrepreneurial investments or its senior officials' investments. Thus, despite promoting transparency, this donation disclosure will not be sufficient to address the concerns of institutional COI.

In sum, unlike COI at the individual-researcher or government advisor level, the Israeli biomedical regulatory scheme does not address the risks of institutional COI. Not only does the regulatory scheme not address institutional COI, but in some respects the regulations regime itself might be intensifying these institutional COI, in light of the requirement to include a representative of the institution's management on the ethics committee. The reason for such a requirement was founded on the grave responsibilities imposed upon the institution's director. Lastly, the statutory disclosure and reporting provision imposed on the industry and the public hospitals will allow more transparency for identifying the prevalence of COI at the institutional level. As discussed in detail below, with a lack of government guidance on the matter, significant inconsistencies were found among the hospitals with regard to interpreting the scope of COI and its consequences. Apparently, with no clear stand on essential institutional COI standards and

⁸³³ See Lifshitz at the Knesset Labor, Welfare & Health Committee *supra* note 190.

⁸³⁴ With regard to physicians, the threshold for disclosure is annual donations of more than 2,500 NIS.

processes, the Israeli regime bequeaths the institutional actors and the public with some fundamentally unresolved questions.

This brief review of the scholarly literature and the regulatory mechanisms has served to highlight a number of issues relating to the definition and use of the concept of institutional COI in the realm of clinical research. Subsequent to the regulatory framework overview, or lack thereof, the following discussion is devoted to the interview data obtained from those in charge of the approval and oversight of clinical trials.

6.3 Institutional COI – The Interview Data

The following section focuses on the data obtained from officials and the MOH and hospital professionals, mainly hospital directors and ethics committee members in charge of the approval and oversight of the clinical trials conducted at their institutions. As discussed in the methodology section in Chapter 1, all interviewees were asked to articulate their experiences regarding two main thematic areas: what constitutes institutional COI; and what actions are taken once institutional COI is identified. To control the interviewees' potential bias and to strengthen the internal validity of this research, the goal was to interview several professionals from the same hospital. This section also weaves in information obtained from the seven sampled hospitals' websites.

Overall, hospital officials interviewed affirmed that their institution is administrating clinical trials for industry, and generating revenues from it. As one would expect, with the lack of regulatory guidance, the interviewees did not find such circumstances as COI concerning or requiring of any action by their institution. In addition, four hospitals out of the seven confirmed having an active R&D department in charge of facilitating technology transfer. Unlike administrating clinical trials for the industry for profit, and despite the lack of any regulatory stance, officials from four of the seven hospitals found that patent holding by a research institution raises concerns for COI. These officials, as discussed below, maintained that their institution was taking measures to eliminate or mitigate against such potential COI. In accordance with the thematic approach to the interviews, the following sections are divided into two: institutional COI definition and identifying processes; and consequences to institutional COI.

6.3.1 *Defining and Assessing Institutional COI*

In view of the lack of a regulatory policy with regard to institutional COI, hospital officials were asked to describe how they defined situations of COI, if at all. Based on the interview data, three different scenarios were discussed during the interviews: administrating clinical trials for the industry; hospital's entrepreneurial interests; and ethical or management decision-making. The following sub-sections describe the interview data in accordance to these three scenarios.

Administrating clinical trials for industry All hospital officials interviewed indicated that their institution was conducting clinical trials for the industry in return for fees required to conduct the trial. Further review of these hospitals' websites supports these claims. In one hospital, the website indicated that more than half of their total research was funded by the biomedical industry, while another indicated that their R&D department was working to ensure further collaboration with industry. The MOH official interviewed estimated that hospitals receive between 15-17 percent of industry-sponsored-trial budgets for each trial conducted at their facilities.⁸³⁵

Only three hospitals – hospital 3, 4 and 7 – mentioned that generating income from running studies for the industry could be perceived as potential institutional COI. The interviewee stated that hospitals always have financial interests in conducting clinical trials.⁸³⁶ Other interviewee indicated that due to the fees they charge, it is only natural that the hospitals have financial interests in specific research and thus will be interested in pushing to conduct more industry funded studies.⁸³⁷ This interviewee along with the interviewee from hospital 4 described⁸³⁸ past occasions where commercial companies were willing to pay thousands of NIS to the hospital for patient recruitment to their study.⁸³⁹ Another interviewee from hospital 3 stated: “the institution's

⁸³⁵ Interview *supra* note 185.

⁸³⁶ Interview with hospital 7 official *supra* note 459.

⁸³⁷ Interview with hospital 3 official *supra* note 474.

⁸³⁸ Interview with hospital 4 official *supra* note 466.

⁸³⁹ Generally, the recruitment process for trial participants imposes ongoing challenges on the commercial trial sponsor who is always eager to finish this process as soon as possible. The pressure to complete the recruitment process quickly is in part due to the fact that any delay may increase the costs of the trial. Also, any delay in the recruitment process will extend the period of the trial, and thus shortens the period during which the commercial sponsor may exclusively market the product before its patents rights are expired. For more information, see Du Val *supra* note 11.

nature is no different from human nature in that they both are interested in selling services and information.”⁸⁴⁰ This interviewee could not find any difference between circumstances of COI resulting from the affiliation between sponsor-investigator and the affiliation between sponsor-hospital.

The three hospitals who acknowledged that recruitment fees or trial administration income may constitute institutional COI, were the same hospitals of the total sampled seven who did not have technology transfer offices in their facilities. As discussed in detail above, the technology transfer offices are responsible for facilitating discovery transfer from the research facilities to the market place. The three hospitals explicitly indicated that their institutions have very few intellectual property rights to their discoveries, and thus the only possible institutional COI they identified were the research-related fees obtained from industry.⁸⁴¹

Other interviewees, from hospitals 1, 2, 5 and 6, did not refer to administration or recruitment fees at all when they were asked to discuss issues of institutional COI. To some extent this omission might be reasonable since the current scheme does not define these circumstances as potential COI, nor do it requires the hospitals to review or manage such COI. As discussed below, the officials from these four hospitals mainly debated whether or not hospital ownership of intellectual property rights to the investigated product being tested at the same hospital should constitute institutional COI.

Hospital's entrepreneurial interests All hospital officials interviewed for this study stated, in some way or another, that their institution owned some or all of the intellectual property (mainly patents) to the inventions conceived by their employees, although the quantity of patents varied. Some interviewees mentioned that their institution held an equity position or had royalty agreements with companies to utilize their developed technology. Four of the seven sampled hospitals employed commercial and research enterprise departments including technology transfer units.⁸⁴² According to the website of one hospital, their business development unit is

⁸⁴⁰ Interview *supra* note 474.

⁸⁴¹ As maintained by official from hospital 3: “As oppose to some other state owned hospitals, who established public corporation to create IP for the hospital, we don't have such R&D department. Therefore, institutional COI is not relevant in this hospital.” Interview *Id.*

⁸⁴² Hospitals 1, 2, 5 and 6.

devoted to facilitate cooperation with industry and license the hospital's patents rights. An interviewee from hospital 6 regarded the technology transfer activities as the hospital's "moral obligation" to obtain the patent rights to their employees' discoveries because this would ensure that these discoveries would reach the marketplace and ultimately benefit the public.⁸⁴³ Practically, these business model mechanisms enable public not-for-profit hospitals to generate revenue from commercialization of their technology.

When interviewees were asked to describe how they defined institutional COI, they expressed diverse opinions on this matter. Table 6.1 below describes the diverse views among the interviewees' definitions of institutional COI resulting from hospitals' entrepreneurial interests. In this table, the interviewees' definitions of institutional COI are divided into two main perspectives: narrow and broad. The notion of whether the definition is broad or narrow was determined by the scope and the range of potential interests considered whenever institutional COI was defined. As the table below shows, the narrow definition shows dependency between the financial interests' value, scope or even the hospital's source of funding and what constitutes institutional COI.

As Table 6.1 below shows, inconsistency was found among the interviewed hospital officials as to what constitutes institutional COI. On the narrower side of the spectrum are interviewees from hospitals 3, 6 and the Director-General of the MOH. While the official from hospital 6 argued that institutional COI depends on the source of funding and the goals of the institution (profit/not-for-profit)⁸⁴⁴, officials from hospital 3 and the Director-General of the MOH acknowledged the concept of institutional COI was a matter of the value or amount of the commercialization opportunity at stake.⁸⁴⁵ The majority of hospital officials interviewed, however, fell into the broader side of the definition spectrum. Namely, four hospitals of the seven, believe that any entrepreneurial interests the hospital has in the product under study at their institution may put the hospital in jeopardy of institutional COI. While one official from

⁸⁴³ Interview with hospital 6 official *supra* note 43.

⁸⁴⁴ Interview *supra* note 463.

⁸⁴⁵ See interviews *supra* note 474 & 521.

hospital 7, made a general comment that hospitals always have financial interests in the studies they conduct.⁸⁴⁶

Table 6.1: Interviewees' Definitions to Institutional COI – Entrepreneurial Interests

Scope of conflicted interest	Hospital number	Defining Institutional COI
Narrow: certain scope or value of financial interests or source of funding.	3	Depending on the number of patents owned by the hospital.
	6	Only applies to private owned for-profit hospitals.
	The Director-General of MOH	A matter of the actual value of profitability.
Broad: every entrepreneurial financial interest.	1, 2 and 5	Hospital financial interests, by virtue of patents/equity holdings, to the research subject matter.
	4	Hospital financial interests, by virtue of equity holdings, to the research subject matter.
	7	Hospitals always have financial interests in the studies they conduct.

Currently there are no data available to pinpoint the number of the hospitals' equity holdings, its equity value or the amount of the financial benefits hospitals in Israel receive from patent licensing arrangements. Four interviewees – the Director-General of the MOH, and officials from hospitals 2, 4 and 6 – mentioned that the value and the extent of such entrepreneurial investments are small. Per the Director-General of the MOH the number of patents owned by the Israeli hospitals is relatively small, and there is not enough profit at stake.⁸⁴⁷ The interviewee from hospital 4 agreed indicating that compared to the U.S. Israel is a relatively small market.⁸⁴⁸ The interviewee from hospital 2 added that multinational pharmaceutical companies are not investing much money in Israeli technology.⁸⁴⁹ The interviewee from hospital 6 stated that their institution currently owned approximately 400 patents for research related inventions. However

⁸⁴⁶ Interview *supra* note 459.

⁸⁴⁷ Interview *supra* note 521.

⁸⁴⁸ Interview *supra* note 466.

⁸⁴⁹ Interview with hospital 2 official *supra* note 436.

he stated that his hospital in fact invests more money on writing the patents than the technology transfer office gets back on the investment.⁸⁵⁰

In view of the estimates showing Israeli hospitals as a relatively small market with allegedly little profit margin, the Director-General of the MOH is convinced that the risks of institutional COI are not yet “matured” in Israeli hospitals compared to those in the U.S.⁸⁵¹ Per his view, the institutional COI is defined by the level of profitability. On the face of it, interviewees from hospitals 3 seem to agree with the Director-General, as they commented that their hospitals hold very few patent rights, and thus did not believe that their institution has institutional COI.⁸⁵² Only one interviewee from hospital 6 stated that institutional COI as a whole is a misconception. He stated that hospitals conducting studies on a product that they also hold patents rights to, has no bearing on the actual conduct of the study or its findings. In his mind, the institution’s financial interests cannot impact decision-making processes of the trial. He further added that this is especially true in not-for-profit institutions. He explained that most hospitals in Israel are not-for-profit institutions and their primary goal is scientific advances and benefits to the patients, not profit. By contrast, in his view, private medical institutions, especially in the U.S., are profit driven institutions where institutional COI might occur.⁸⁵³

Four interviewees from hospitals 1, 2, 4 and 5, however, seemed to disagree with this view as is shown in Table 6.1. These interviewees indicated that hospitals, regardless of their funding sources, holding patents rights to the investigational product or holding equity positions for the subject matter they study, might in fact constitute institutional COI. They argued that such scenarios may warrant action taken by the institutions.⁸⁵⁴ The implications of such determinations vary among these institutions as discussed below. Interviewee from hospital 7 made a general comment that hospitals always have financial interests in the trials they conduct,

⁸⁵⁰ Interview *supra* note 463.

⁸⁵¹ Interview *supra* note 521.

⁸⁵² Interview *supra* note 474.

⁸⁵³ Interview *supra* note 463.

⁸⁵⁴ Interviews with officials from hospitals 1, 2, 4 & 5, at the officials offices at the hospital, Israel (August 30th & 31st, September 7th & 11th 2010 respectively).

but could not provide any specific definition as to when such interests became institutional COI, if in fact they ever did.⁸⁵⁵

Ethical and management decision-making As discussed above, the biomedical regulations require the institutional ethics committee – Helsinki committee – to include a representative of the institution’s management. The interviewees were divided with regard to the role that they believed the management representative played in the ethical decision-making process. On one side of the spectrum, officials from hospitals 4, 6 and the Director-General of the MOH argued that the management representative role did not constitute representing the commercial interests of the hospitals, but rather to contribute to the ethical aspect of the discussion. The interviewee from hospital 4 – who serves on the Helsinki committee as the management rep – remembered occasions, for example, where the committee discussed research applications for which he knew his hospital was offered cash rewards for every participant they recruited. He explained that in these cases, he forced himself not to take part in the discussion as he found it: “hard to separate my own greed and my ethics evaluator responsibilities.”⁸⁵⁶ Seemingly, the interviewee from hospital 6 agreed with this view. He indicated that when he served in the past as the management rep in the ethics committee, he used to “forget” that he actually represented the management interests to focus on the ethical aspects of the study.⁸⁵⁷

On the other side of the spectrum, are interviewees from hospitals 1, 2, 3, 7 and the MOH official. They believe that the management rep is in fact representing the hospital’s financial and commercial interests among other interests. The official from hospital 1 explained that as a former management rep in the Helsinki committee, he used to deal with the economic elements of the research, including the hospital’s intellectual property rights (if applicable), in order to protect the institution’s interests.⁸⁵⁸ Officials from hospitals 2, 3, 7 and the MOH official seem to agree, indicating that the management rep’s role was to represent both the economic and ethical aspects of the trial.⁸⁵⁹ The interviewee from hospital 7 explained that the management rep, like

⁸⁵⁵ Interview *supra* note 459.

⁸⁵⁶ Interview *supra* note 466.

⁸⁵⁷ Interview *supra* note 43.

⁸⁵⁸ Interview *supra* note 456.

⁸⁵⁹ Interviews with officials from hospitals 2 & 3, at the officials’ offices at the hospital, Israel (August 31st & September 2nd 2010 respectively).

the Helsinki committee as a whole, acts as the advisory arm for the director of the hospital, to advise him or her whether to accept or deny the proposed research application.⁸⁶⁰ The MOH official further commented that it is okay to have a representative to protect the hospital’s management interests, as long as other interests are also represented in the committee, such as public interests being represented by legal professionals, scientists etc.⁸⁶¹

6.3.2 *Consequences of Institutional COI*

Administering clinical trials for industry As discussed above, despite the fact that all hospital officials interviewed indicated that their institution is conducting clinical trials for industry in return for fees, only three hospitals – hospital 3, 4 and 7 – mentioned that this might constitute potential institutional COI. However, none of these interviewees, or the others for that matter, described any policy, procedure or mechanism in place to address such COI. In other words, even though some interviewees believed that this scenario might be problematic at the institution level, the hospitals are taking no actions to address it.

Hospital’s entrepreneurial interests Parallel to the diverse definitions given by the various interviewees, the interviewees described different approaches to addressing institutional COI risks. In accordance to the interview data, a direct correlation was found between the scope of the institutional COI definition and the scope of measures taken by the hospitals to minimize it. Namely, the more narrow the definition of COI the less likely that the institution will enforce measures to eliminate it. Table 6.2 below compares the interviewees’ diverse approaches to the consequences of institutional COI with their definition thereof.

Table 6.2: Definitions and Consequences to Institutional COI – Entrepreneurial Interests

Scope of conflicted interest	Hospital number	Defining Institutional COI	Consequences to Institutional COI
Narrow: certain scope or value of financial interests or source of funding.	3	Depending on the number of patents owned by the hospital.	No course of action.
	6	Only applies to private owned for-profit hospitals.	
	The Director-	A matter of the actual value of	

⁸⁶⁰ Interview *supra* note 459.

⁸⁶¹ Interview *supra* note 177.

	General of MOH	profitability.	
Broad: every entrepreneurial financial interest.	1 and 2	Hospital financial interests, by virtue of patents/equity holdings, to the research subject matter.	Outsourcing to another research institution.
	5	Hospital financial interests, by virtue of patents/equity holdings, to the research subject matter.	Need to address it in due time.
	4	Hospital financial interests, by virtue of equity holdings, to the research subject matter.	Strict scientific and ethical review by the Helsinki committee.
	7	Hospitals always have financial interests in the studies they conduct.	No course of action.

Not surprisingly, the interviewees who ascribed to the narrow definition of institutional COI did not find it necessary to have policies, measures or actions taken by the institution. Essentially, the official from hospital 6 who could not discern the notion of institutional COI within not-for-profit institutions did not see any reason to attempt to eliminate or manage these interests. He was determined that in not-for-profit institutions, the entrepreneurial interests of the institution could not affect the conduct, findings or the reporting of the trial.⁸⁶² Moreover, neither the officials from hospital 3 nor the Director-General of the MOH who argued that the institutional COI is not yet matured in Israel due to the small size of the actual investment, found it necessary to address it at this time.⁸⁶³

The interviewees who ascribed the broad definition of institutional COI to the hospital's entrepreneurial interests (interviewees from hospitals 1, 2, 4 and 5), described a number of additional actions taken at their institution in the attempt to eliminate COI. One strategy frequently raised by three of the four interviewees was to outsource the specific clinical trial to other non conflicted institutions. An interviewee from hospital 2 further explained that outsourcing the trial to a non-interested research institution would contribute to the external validity of the research findings. In his mind, "this is very basic. We have an interest in the drug that we develop here being tested elsewhere to make the research findings stronger. It is in the

⁸⁶² Interview *supra* note 463.

⁸⁶³ Interviews *supra* notes 474 & 521.

financial interest of the hospital to conduct the research outside; otherwise it will be a waste of money.”⁸⁶⁴

An interviewee from hospital 5 seemed to disagree with this stance. In his opinion, outsourcing the trial to another institution, although possible, would not be fair to the hospital’s patients. He argued that participating in a clinical trial, especially with products that have commercial potential, benefits the patients-participants who get to enjoy the product before it gets to the market. Thus, he believes that not allowing the hospital’s patients the access to such products first, is not preferable.⁸⁶⁵ He then raised another possible solution in which the conflicted hospital gets to conduct the trial subject to an independent body monitoring and oversight. He mentioned that these solutions need to be considered in due time when the MOH finally formalizes its initiative to enable the state-owned hospitals to retain the intellectual rights to their inventions. In view of the above, although the interviewee from hospital 5 was in agreement with the scope of the definition of institutional COI as others in this group, his institution currently takes no actions to address it.⁸⁶⁶

The last interviewee, who ascribed to the broad definition of institutional COI from hospital 4, described another course of action. In his view, if his institution holds equity positions in a startup company potentially benefiting from the specific research, then the Helsinki committee is stricter in its scientific and ethical evaluation.⁸⁶⁷

Ethical and management decision-making As discussed above, inconsistency was found among the interviewees as to the role the management representative plays in the ethical decision-making process. Despite such clear inconsistency, greater consensus was found with regard to possible effects of having a management representative on the ethics committee. The majority of interviewees from both sides of the spectrum maintained, that in fact the presence of the management official has no bearing on the objectivity of the committee. The majority of the interviewees believed that the Helsinki committee is well balanced having many professionals

⁸⁶⁴ Interview *supra* note 436.

⁸⁶⁵ Interview *supra* note 505.

⁸⁶⁶ *Id.*

⁸⁶⁷ Interview *supra* note 466.

with different interests and approaches to counterbalance any commercial and management interests. Per their view, the different members of the Helsinki committee are able to use their joint expertise to assess the scientific, ethical and legal legitimacy of every proposed trial protocol.

Not surprisingly, the group of professionals who viewed the role of the management representative as strictly ethical, i.e. officials from hospitals 4, 6 and the MOH Director-General, could not see any possible risks for bias. As an interviewee from hospital 6 explained, “there is a clear separation between Helsinki and the hospital’s management. There will not be any situation where the hospital will push for research approval due to financial interests.”⁸⁶⁸ An interviewee from hospital 4, who currently serves as the management rep in the Helsinki committee, explained that although he understands the possible bias in situations where the hospital has financial interests in the research proposal, he nevertheless believes that the management representative will be able to override such bias while remaining passive or quiet during the ethical discussion.⁸⁶⁹

More interesting are the views expressed by the group of interviewees who ascribed to the view that the management rep does protect the institution’s financial interests. This position was taken by officials from hospitals 1, 2, 3, 7 and the MOH official. For the most part, the interviewees agreed that encompassing the hospital’s financial interests within the ethical evaluation is well balanced with other interests. Per the interviewee from hospital 1 (who had served as a management rep in the past) “there are no veto rights in the committee for any member... even if the management rep is aware of the hospital’s commercial interests in a specific trial, his or her voice will not have more weight in the committee’s decisions than any other member of the committee.”⁸⁷⁰ The interviewee from hospital 3 added “There are enough members in the ethics committee that do not have personal gain at stake, and they are the guard dogs in the committee.”⁸⁷¹ The interviewee from hospital 2 agreed maintaining that the management rep has the right, like other member of the committee, to appeal the decision made by the committee or

⁸⁶⁸ Interview *supra* note 463.

⁸⁶⁹ Interview *supra* note 466.

⁸⁷⁰ Interview *supra* note 456.

⁸⁷¹ Interview *supra* note 474.

to ask for further review. She indicated though that in their committee; the management rep rarely requests further view or appeals the decision.⁸⁷²

Notably, three interviewees – from hospital 3, 6 and 7 – noted that although the committee is ethically balanced to some extent, having a management rep is problematic. Two interviewees, from hospital 6 and 7 argued that this is an “unnecessary function”.⁸⁷³ The interviewee from hospital 7 explained that the Helsinki committee should be comprised of people with clinical trial skills, mainly bioethicists and public representatives.⁸⁷⁴ Only one interviewee, from hospital 3, maintained that such representation may cause concerns for bias. In her view “the ethics committee should not include any commercial aspects. The management rep can incorporate the institution’s commercial interests even without being aware of doing so. This is not desirable.”⁸⁷⁵ Lastly, the interview data indicated that in two hospitals sampled for this study⁸⁷⁶, the lack of separation between the ethical and commercial aspects is even more comprehensive. As the officials from these two hospitals explained, the Helsinki committee and the technology transfer office are both governed under the supervision of the same individual – the head of the R&D department. Hospital officials explained, “The hospital R&D department is responsible for the technology transfer office and also for the ethical side as it is responsible for the Helsinki committee. The head of the R&D department is responsible for the review and approval of the commercial contracts with the commercial companies, and it also approves the ethical process.” As discussed below, the need to clearly separate the direct management involvement within the ethical processes is essential in order to protect the public’s trust.

6.4 Discussion and Analysis of Interview Findings

The abovementioned review of the interview data and regulatory mechanisms has served to underline a number of issues relating to the practical use of the COI concept in biomedical research involving human subjects at the research institution level. Essentially, the regulatory framework relies on the institutional reviewers to safeguard the primary principles of research.

⁸⁷² Interview *supra* note 436.

⁸⁷³ Interview *supra* note 43 & 459.

⁸⁷⁴ *Id.*

⁸⁷⁵ Interview *supra* note 474.

⁸⁷⁶ In order to protect the anonymity of the interviewee participating in this study, the Author decided not to include the number of the hospitals indicated in this section.

Despite general government oversight, the hospitals mostly self-regulate the approval and monitoring of the clinical trials conducted at their premises. Concurrently with the backdrop of such strong professional-institutional control, Israel has been undergoing a profound transformation of privatization, influenced by the U.S. model, enhancing the competitive research enterprise within public-not-for-profit hospitals. Based on the government's advancing privatization model, the current regulatory landscape and the interview data, the next sections will discuss issues relating to the implementation of the current governance framework in terms of roles, standards and responsibilities.

6.4.1 Intertwined Ethical and Commercial Evaluations - Lack of Organizational Barriers

As discussed above, the current regulatory regime requires the representation of the hospital's management within the ethical evaluation of clinical research. In fact, without such representation there is no legal quorum to the Helsinki committee's approval processes. All hospital officials interviewed assured that the management representative participated in the ethical and scientific assessment of research applications.⁸⁷⁷ Disagreement, however, was found among the interviewees as to whether this representative was also responsible for considering the hospital's commercial interests. While some viewed that a management rep's purview is strictly to safeguard ethics (hospitals 4, 6 and the Director-General of the MOH), the majority, including present and past management reps (hospitals 1, 2, 3, 7 and the MOH official), believed that his or her responsibility is also to protect the financial interests of the hospital.

Rather than restricting clinical trial approval mechanisms to scientific and ethical considerations, the regulatory system appears to ensure joint assessment of factors related to ethics and profit. Nonetheless, the majority of the interviewees maintained that such joint assessment does not create concerns for bias as the ethical-approval process is adequately balanced. Only one interviewee, who currently serves as the management rep at hospital 3, argued that such joint evaluation is not desired as it may create bias. Two other interviewees, from hospitals 6 and 7, argued that such regulatory requirement is unnecessary and redundant.

⁸⁷⁷ Interviews with officials from hospitals 1 through 7 (August-September 2010).

Moreover, as the interview data showed, in two hospitals the ethics and profit assessment is even more prevalent in view of the supervisory structure of their organization. In these two hospitals, not only is the management present in the ethics committee, but also the head of the R&D department is responsible to review and approve technology transfer contracts with the industry, and at the same time to review and approve the ethical evaluations made by the Helsinki committee. In both hospitals, the trial approval mechanism imposed by the regulations upon the hospital director⁸⁷⁸ was delegated to the head of the R&D department.

From a regulatory perspective, can an intertwined ethical and commercial paradigm be adequate to protect the primary goals of clinical research? In the U.S., for example, the joint report issued by the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU) has offered some guidance on the issue.⁸⁷⁹ In their 2008 report, the AAMC-AAU addressed the concerns of institutional COI at research institutions in view of the increased public scrutiny over the strong ties between academic institutions and the biomedical industry. The AAU and AAMC recommended that institutions create clear organizational barriers separating the responsibility for oversight of human participants' studies from the responsibility for institutional investment endeavors and technology transfer plans. The rationale for such organizational policy is to prevent the appearance or actual impact of financial considerations upon the institution's research-academic decisions.⁸⁸⁰ The main concern is that the institution's financial interests could affect or reasonably appear to affect the institution's practices, including the conduct, review, or oversight of human research. The AAU and AAMC warn that failing to create such an organizational "firewall" will significantly amplify "...the risks of compromising the safety of human subjects⁸⁸¹ and the integrity of the research performed..."⁸⁸²

It is important thus, that the direct control of the department in charge of technology transfer and other institutional commercial interests, be clearly separated from the unit responsible for research approval and oversight. By the same measure, it is important to create well-defined

⁸⁷⁸ As discussed in details in chapter 5, certain trial approval authorities were imposed on the hospital's director, see Public Health Regulations *supra* note 138 at §2 - 4.

⁸⁷⁹ See the AAMC & AAU 2008 report *supra* note 234.

⁸⁸⁰ See Du Val *supra* note 11.

⁸⁸¹ The most common example used by the literature illustrating how institutional COI can have dangerous impact on the safety of trial participants is the death of Jesse Gelsinger case discussed in mentioned *supra* note 215.

⁸⁸² See the AAMC-AAU report *supra* note 234 at chapter 2 §C(1).

distinctions between the ethical and scientific considerations and the institutional financial interests at the ethics committee level.

Incorporating management representation as a vital part of the ethical deliberations is problematic. Such practice can bring into question the integrity of the scientific and ethical decisions made by the institutional committee during the course of the approval and oversight of the trial. Notably, this study does not argue that the decisions made by the Helsinki committees in Israel were biased, nor does it question the integrity of its members. The intertwined financial incentives with the ethical consideration may create concerns for the perception of bias, even if bias was never a real factor. Furthermore, the majority of the interviewees believed that the management rep is responsible to consider the hospital's financial interests at the time of ethical and scientific assessment. Given such practice, concerns for implied bias is apparent.

Such bias or perception of bias is even more alarming in view of the physiological studies showing how people tend to overestimate their ability to ignore their self-interest, convinced that the conflicting interest has a lower impact on their decision than it actually does.⁸⁸³ The perception of bias, as the AAMC-AUU warn, may produce public mistrust in the endeavor of the research enterprise, questioning the research findings and the extent of protection for the safety of participants.⁸⁸⁴

In order to control the risks of financial institutional COI, enabling real separation of the ethical and commercial functions, the literature recommends creating an independent COI institutional committee. Such an autonomous committee would be in charge of conducting impartial review of the institution's financial interests and whether such interests may create concerns for COI in research at the institution. The emphasized requirement is that this separate committee act as an

⁸⁸³ In his article, Yuval Feldman, a well-known Israeli scholar, discussed recent psychology literature suggesting that individuals are usually unaware of how the self-interest impacts their actions. For example, Feldman review a series of studies conducted by Max Bazerman at el to explore issues of objectivity in accountants audit reports. Among the incentives tested where whether prior acquaintance with the audited customer had any impact on the decision-making process. These studies found that even when a few seconds meeting with the customer, had major impact on the accountant's decision. Interestingly, when the accountants were asked about whether that impacted their decision, they stated that they were unaware of such influence. For more information see Feldman *supra* note 76 at 81.

⁸⁸⁴ See the AAMC-AUU report *supra* note 234.

“independent watchdog”, which necessitates its members be autonomous from protecting the institution’s financial security or benefiting from the financial investment they review.⁸⁸⁵

6.4.2 The Government Created “Hybridized Hospitals” and Lack of Regulatory Response to Institutional COI

Global entrepreneurialism of public biomedical research and close ties with the private sector has introduced powerful financial incentives into the public arena. In Israel, through powerful forces of privatization influenced by the U.S. model, the competitive research enterprise was enhanced. The Israeli current regulatory scheme has been gradually allowing entrepreneurial incentives of medical research in public not-for-profit institutions to flourish. This new class of hybridized hospitals, equipped with a new mission of capitalizing on public funded discoveries⁸⁸⁶ has raise concerns for bias by virtue of institutional COI.

Unlike COI at the individual researcher or government advisor levels, the Israeli regime has no statutory provisions that directly govern hospitals’ COI. On the face of it, one can argue that despite the growing entrepreneurial opportunities encouraged by the government, these have not yet matured into institutional COI so as to be recognized by the Israeli scheme as potentially risking the primary objectives of research. This was the perception of the Director-general of the MOH who argued that the current low value of the hospitals’ investments should not merit any regulatory response.⁸⁸⁷ The interview data however, does not seems to support such a view. Four out of the seven hospital officials, from hospitals 1, 2, 4 and 5, maintained that the hospitals’ financial interests, by virtue of patents or equity holdings, for the research subject matter should constitute institutional COI. That said, only three hospitals (hospitals 1, 2 and 4) indicated that their institutions were taking active measures, whether by the Helsinki review process or the

⁸⁸⁵ For more information about the possible solutions to institutional COI in research institutions, see Liang & Mackey *supra* note 595; and Barnes & Florencio *supra* note 23.

⁸⁸⁶ Henry Etzkowitz conceptualizes the new mission of universities in the U.S. in terms of “capitalization of knowledge”, as the academic institutions have been working to translate knowledge into public use. See Henry Etzkowitz, From Conflict to Confluence of Interest: The Coevolution of Academic Entrepreneurship & Intellectual Property Rights, In Trust & Integrity in Biomedical Research 74-75 (Thomas H. Murray & Josephine Johnston ed. John Hopkins 2010).

⁸⁸⁷ Interview *supra* note 521.

decision to outsource the trial to another institution to manage or mitigate such institutional COI. Others indicated that no further actions were taken at their institutions.⁸⁸⁸

Such a wide variations with regard to adjusting to the emerging institutional COI among research institutions was also found in the U.S. despite regulatory agency and professional associations' guidance on the issue. Generally, the Office of Inspector General (OIG)⁸⁸⁹, the joint task force of the AAMC-AAU⁸⁹⁰ and the IOM report⁸⁹¹ have all urged research institutions to develop and apply comprehensive institutional COI policies. The IOM report, for example, endorsed medical institutions to effectively manage their institutional COI and allow transparency in their efforts to do so. The IOM report also called the institution's board and senior officials to be accountable for ensuring their institution is indeed managing its own interests.⁸⁹²

However, studies show that U.S. research institutions have not given adequate attention to institutional COI. Per a survey conducted by Ehringhaus et al., only 38 percent of medical schools established institutional COI policies applicable to financial interests held at their institutions.⁸⁹³ A much higher rate, 69 percent, adopted institutional COI policies applicable to their senior officials, and 81 percent established policies applicable to their ethics committee (IRB) members.⁸⁹⁴ This relatively low percentage of institutional COI policies adopted by U.S. medical schools stands in a direct contrast to the more stringent policies adopted to address COI at the individual level.⁸⁹⁵ Another study conducted by the Office of Inspector General (OIG) published in 2011, reported that 70 of 156 responding NIH grantee institutions have written policies and procedures addressing institutional COI.⁸⁹⁶ The report also maintained that

⁸⁸⁸ See Table 6.2 above.

⁸⁸⁹ See Office of Inspector Gen., Dep't of Health & Human Servs., National Institute of Health: Conflict of Interest in Extramural Research (January 2008) & Institutional Conflict of Interest at NIH Grantees (January 2011), available at <http://oig.hhs.gov/oei/reports/oei-03-06-00460.pdf> & <http://oig.hhs.gov/oei/reports/oei-03-09-00480.asp> respectively (last visited Sept. 7, 2012).

⁸⁹⁰ The AAMC-AAU report *supra* note 234.

⁸⁹¹ See the IOM report *supra* note 32.

⁸⁹² *Id.* at 228-229.

⁸⁹³ In this survey Ehringhaus et al. conducted a national survey of the deans of 125 accredited allopathic U.S. medical schools administered during 2006. See Susan H. Ehringhaus et al., Responses of Medical Schools to Institutional Conflicts of Interest, 299 JAMA 665, 665 (2008).

⁸⁹⁴ *Id.*

⁸⁹⁵ The IOM maintained that less attention was attributed to institutional COI as oppose to individual COI, and thus less evidence was collected to its characteristics and impacts. See the IOM report *supra* note 32 at 219.

⁸⁹⁶ The OIG 2011 report *supra* note 889.

institutions, who had written intuitional COI policies and procedures, were more likely to identify institutional COI than those who did not.⁸⁹⁷

Some scholars regard the U.S. current system as fragmented due to the incoherent responses to institutional COI, its slow adoption rates, and the variations found in the policies of institutional COI in the institutions who did address it.⁸⁹⁸ In the wake of the emerging data showing inconsistency in institutional COI policies and procedures, and in view of the increasing public and scholarly attention to the topic, the OIG⁸⁹⁹ and IOM report,⁹⁰⁰ have advocated that the federal government institute clear rules governing institutional COI. However, despite such clear recommendations, the federal government has not addressed institutional COI.⁹⁰¹ Per David Korn, the decision of the NIH not to include any rules for institutional COI was due to the research community's pressure convincing the agency that including such an explicit requirement "would still be premature".⁹⁰²

In Israel the variations found among the hospitals in responding to institutional COI is problematic. It may provide confusing messages to the public who are left to ponder why some hospitals consider holding institutional financial interests in the research they conduct as being risky while others do not. Moreover, scant information is available about the scope and nature of the ties between public not-for-profit hospitals and the biomedical industry in Israel. There are no collected data with regard to the type and amount of payments, grants or donations received from the industry, as well as no published information regarding the hospitals' ownership interests in for-profit corporations, patents and/or the investments made by the senior officials at the institutions.

⁸⁹⁷ The OIG 2011 report showed that the most common type of institutional conflict identified by the respondent was the institutions' holding equity in non-publicly held companies. Most used strategy used by the institutions to address the institutional COI was disclosure. See *Id.*

⁸⁹⁸ See Liang & Mackey *supra* note 595.

⁸⁹⁹ In two reports, the OIG recommended the NIH to promulgate regulations that address institutional financial conflicts of interest, and to require detailed disclosure of institutional COI. See the OIG 2008 & 2011 reports *supra* note 889.

⁹⁰⁰ See the IOM report *supra* note 32 at 228-229.

⁹⁰¹ The federal regulations currently do not require research institutions to address the risks of institutional COI. In 2010 the NIH issued ANPRM soliciting responses from the research community regarding possible changes to the NIH COI 1995 Rules. The new NIH 2011 COI rules indeed strengthened its financial COI principles, most noticeable was the absent the requirement to address institutional COI.

⁹⁰² See David Korn *supra* note 397.

At a time when the government is actively encouraging not-for-profit government-owned hospitals to financially gain from their new publicly funded discoveries, the absence of such empirical data is disturbing. With the government initiative to encourage hospitals to strengthen their collaborations with industry and expend their own entrepreneurial interests, assessment of its implications is required. At minimum, creating hybridized research institutions with powerful financial incentives requires re-assessment of the organizational framework and infrastructure to address potential institutional COI such policy creates.

6.5 Conclusion

The regulatory framework relies on institutional reviewers to safeguard the primary principles of clinical research involving human subjects. Despite general government oversight, the hospitals mostly self-regulate the approval and monitoring of the clinical trials conducted on their premises. Israel has been undergoing a profound transformation toward privatization, influenced by the U.S. model, enhancing the competitive research enterprise within public-not-for-profit hospitals. Additionally, the Israeli government has been advancing policy enabling commercialization of intellectual property generated with public research funds.

Despite the potential for scientific progress, such government initiatives may also encourage strong collaboration with the industry promoting a competitive and entrepreneurial research enterprise. Data suggest that the industry support of clinical research conducted in non-profit institutions in Israel, including government owned hospitals, is on the rise. Based on the government's advancing privatization model and its encouragement of entrepreneurialism of biomedical research, the current design of safeguards and the designation of stakeholders in charge of enforcing regulations are now being called into question.

The new entrepreneurial, hybridized hospitals raise concerns for institutional COI by virtue of their position in safeguarding the primary goals of research. The main concern is that potential biases within the institutional decision-making practices will jeopardize the health of research subjects, research integrity, and public trust. Unlike COI at the individual-researcher or government advisor level, the Israeli biomedical regulatory scheme does not address the risks of

institutional COI. Not only does the regulatory scheme not address institutional COI, but in some respects the regulatory regime itself might be intensifying this institutional COI, in light of the requirement to include a representative affiliated with the institution's management on the ethics committee.

Given the lack of government guidance on the matter, it was imperative to obtain the hospital officials' perspectives on COI at the institutional level. Three different scenarios were identified as COI related during the interview phase: administrating clinical trials for the industry; hospital's entrepreneurial interests; and ethical and management decision-making. Overall, hospital officials interviewed affirmed that their institution is administrating clinical trials for industry and generating revenues from it. As one would expect with the lack of regulatory guidance, the interviewees did not find such circumstances as being inherent of COI or as requiring of any action by their institution. In addition, four hospitals out of the seven confirmed having active R&D departments in charge of facilitating technology transfer between their institution and the pharmaceutical industry. Unlike administrating clinical trials for profit, and despite lack of regulatory governance, officials from four of the seven hospitals found patent holding by a research institution as concern for COI. However, inconsistency was found among these institutions as to the measures required for eliminating or mitigating against such potential COI.

Moreover, inconsistency was found among the interviewees as to the role the management representative played in the ethical decision-making process. However, despite such clear inconsistency, consensus was found among the interviewees that management official does not impact objectivity in the decision making process of the committee. Only three officials held the view that while the committee is ethically balanced, having a management rep is problematic. Lastly, interview data indicated that in two hospitals the ethical and profitable joint assessment is arguably even more prevalent in view of the supervisory structure of their organization. In these two hospitals, not only is the management present on the ethics committee, but the head of the R&D department is responsible for reviewing and approving technology transfer contracts with industry, and at the same time reviewing and approving the ethical evaluations made by the Helsinki committee.

The review of COI at the research institution level in Israel has served to underscore a number of research governance issues. Issues discussed in this chapter were based on interview information and regulatory mechanisms and include the following main areas of concern: rather than restricting clinical trial approval mechanisms to scientific and ethical considerations, the current regulatory regime appears to ensure joint assessment of factors related to ethics and profit; some hospitals lacked organizational barriers separating the responsibility for oversight of human participants' studies from the responsibility for institutional investment endeavors and technology transfer program; and government created hybridized research institutions with profound financial incentives call into question the current regulatory and organizational framework and infrastructure and its ability to deal with potential institutional COI.

CHAPTER 7: Comparative Analysis of the U.S. Biomedical COI Regime and Policy Recommendations for the Israeli COI Regime

In light of the critiques discussed in Chapters 4-6 with regard to the Israeli COI regulatory regime, in five sections this chapter explores the U.S. experience attending to similar COI challenges. The reference to the U.S. COI model only serves the purpose for comparative analysis and policy recommendations for the Israeli system. The comparative review of the U.S. regime explored in this chapter parallels the analysis of three areas of potential conflict discussed in Chapters 4-6: researcher; research reviewer; and institutional. Section 7.1 begins with the objectives of the comparative analysis including the reasons for choosing the U.S. system. Section 7.2 explores current U.S. regulations, policies and guidance addressing COI at the individual researcher level. Important differences between Israeli and U.S. regulatory schemes in regard to investigator's financial disclosure provisions are highlighted and analyzed.

Following the review of the U.S. model, section 7.2 proceeds to confer the issue found in the Israeli regime related to investigators' COI and makes policy recommendations based on the comparative analysis. Section 7.3 explores the existing U.S. regulations, policies and guidance with respect to institutional ethics committees and government advisory committees. Then section 7.3 discusses the issues found in the Israeli regime related to government advisors and members of the Helsinki committee, and makes policy recommendations based on the comparative analysis. Section 7.4 explores the existing U.S. policies and guidance with respect to institutional COI. This section will conclude with policy recommendations for the Israeli scheme.

The proposed recommendations discussed in this chapter, aim to promote transparency and accountability to enhance scrutiny and uniformity to the Israeli biomedical scheme. Consistent with such objectives, these policy recommendations include key elements of COI disclosure applicable to all stakeholders involved in human participants' research, as well as clear definitions, standards and a structural basis for identifying and evaluating COI circumstances. It further emphasizes that any consideration for policy recommendation necessitates considerable

discussion among scholars, scientists, government officials and the public to best foster a thorough and consistent governance framework for COI issues in the biomedical research arena in Israel. Section 7.5 summarizes and concludes the main findings.

7.1 Introduction

As discussed in previous chapters, this thesis examines the governance, operations and practices of Israel's biomedical scheme which safeguard against risks associated with COIs in biomedical research. A review of the relatively new Israeli regulatory regime highlights the complexity of COI in medical research which attempts to protect ethical conduct. Chapters 4-6 discuss in detail current Israeli challenges in responding to COI issues. In the attempt to address these challenges, this chapter draws on lessons from U.S. experience attending to similar COI challenges. This chapter discusses some of the current issues ascribed to financial COI and offers a baseline proposal for policy change. This chapter does not, however, provide an overview of the U.S. biomedical regulatory regime. The reference to the U.S. COI model only serves the purpose for comparative analysis and policy recommendations for the Israeli system.

As discussed in Chapter 1, the U.S. biomedical model functions suitably for comparative analysis due to the fact that it developed over the course of more than two decades, during which time the model developed with regard to ethical evaluation of COI. There is much material to draw from, including surveys, empirical studies and scholarly articles. Additionally, both Israel and the U.S. adhere to similar ethical principles and similar regulatory frameworks for research approval and oversight.⁹⁰³ Finally, Israel and the U.S. collaborate intensely on biotech innovation. Many Israeli physicians and researchers are trained via fellowships in the U.S., and most of Israel's medical policies are aligned with those of the U.S.

The comparative review of the existing U.S. regime, explored in sub-sections 7.2 – 7.4 below, is consistent with the analysis of three areas of potential conflict discussed in Chapters 4-6: researcher; research reviewer; and research institution. Notably, these areas of conflict in the U.S. can also be differentiated based upon the scope of the federal regulations and public and

⁹⁰³ Like the U.S. FDA, the Israeli regulatory regime explicitly acknowledged and adopted the provisions of the Good Clinical Practice Guidelines issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). See ICH GCP *supra* note 52.

scholarly scrutiny. While early on research investigators and government advisors were subject to significant media and public scrutiny for COI⁹⁰⁴, the members of the institutional ethics committee (IRB) and the research institutions were more or less under the radar. This explains, as the comparative analysis below shows, the extensive federal regulatory response to COI at the investigator and FDA advisor levels, and the little to almost no response to COI for the IRBs and institutions. With public and scholarly attention having now shifted in the U.S. to COI at the institution level⁹⁰⁵, many governmental and non-governmental organizations in the U.S. call for the federal government to step in to respond.⁹⁰⁶

Section 7.2 below serves to underline existing U.S. regulations, policies and guidance in the attempt to address the COI related challenges found under the Israeli regime at the individual researcher level. The comparative component and the policy recommendations in this section are based on two U.S. federal agencies' regulations, the FDA and the NIH, as well as other guidance issued by the AAMC, the AAU and the IOM promoting transparency and accountability by virtue of disclosure and COI management. Lastly, section 7.2 will conclude with policy recommendations for the Israeli scheme.

7.2 COI at the Biomedical Researcher Level – Comparative Review

In an attempt to address concerns relating to the effects of investigators' financial COI, the following federal agencies, professional and nonprofit organizations have promulgated regulations and policies to maintain validity of the scientific data and to safeguard human subjects. The regulatory agencies include the NIH, and the FDA; and the professional and nonprofit organization include the AAMC, the AAU, and the IOM. Although notable differences exist among these regulations and guidelines, all stress detailed financial disclosure and COI management over the creation of strict prohibition policies. Below are the key elements found in each of the mentioned regulations and guidelines.

⁹⁰⁴ See the IOM report *supra* note 32.

⁹⁰⁵ See Lemmens *supra* note 29 at 747.

⁹⁰⁶ See for example the OIG reports recommending the NIH to promulgate regulations that address institutional financial conflicts of interest, and to require detailed disclosure of institutional COI. The OIG 2008 & 2011 reports *supra* note 889.

7.2.1 U.S. FDA Financial Disclosure Regulations versus Israeli Investigator-Sponsor Affiliation Provision

As part of its mission to ensure safety and efficacy of drugs, medical devices and biological products, the FDA regulates clinical trials involving human participants.⁹⁰⁷ The FDA's financial disclosure regulations seek to ensure the adequacy of the clinical trial and its findings.⁹⁰⁸ The FDA may consider the trial or the data thereof inadequate if "...appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias."⁹⁰⁹

The FDA's financial disclosure regulations require *sponsors* to satisfy three key requirements as a precondition to receiving the agency's marketing approval:

- 1) Disclosing information regarding all the investigators taking part in the clinical study as well as their financial interests.⁹¹⁰ Although the investigators are not required to provide this information to the FDA directly, they are obligated to provide the sponsor with sufficient financial information⁹¹¹ to enable the sponsor to meet its disclosure obligations.⁹¹² Per the regulations, the sponsor must disclose the following financial information:
 - Financial arrangement between the sponsor and investigator whereby the value of the compensation could be influenced by the outcome of the study;⁹¹³
 - "Any significant payments of other sorts"⁹¹⁴ including grants to fund ongoing research, equipment, and consultation fees;⁹¹⁵
 - Any proprietary interest⁹¹⁶ in the tested product held by investigator involved in a study;

⁹⁰⁷ The FDA regulations are directed at the protection of human participants in any research conducted for marketing approval for products regulated by the FDA. See 21 CFR §50.1.

⁹⁰⁸ The FDA's main concern is the risk that financial associations might jeopardize the validity of the data submitted to support the marketing application. See Jesse A. Goldner, Childress Lecture: Regulating Conflict of Interest in Research: The Paper Tiger Needs Real Teeth, 53 St. Louis L.J. 1211 (2009).

⁹⁰⁹ 21 CFR §54.1(b).

⁹¹⁰ 21 CFR §54.4. The trial sponsors are required to provide this information prior to the conclusion of the trial as part of the product's marketing approval process. See Kathleen M. Boozang, Carl H. Coleman & Kate Greenwood, An Argument Against Embedding Conflicts of Interest Disclosures in Informed Consent, Vol. 4, No. 3, J. Health & Life Sci. L. (2011).

⁹¹¹ The trial investigator must "...promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study." 21 CFR §54.4(b).

⁹¹² *Id.* at §54.4(b)

⁹¹³ *Id.* at §54.4(a)(3)(i).

⁹¹⁴ Significant payments of other sorts are defined as payments made by sponsor to investigator or the institution exceeding 25,000 USD excluding the costs of conducting the specific clinical study. *Id.* at §54.2(f).

⁹¹⁵ *Id.* at §54.4(a)(3)(ii).

- Any significant equity interest⁹¹⁷ in the sponsor of the covered study held by any clinical investigator involved in any clinical study;
- 2) Informing the FDA of all the steps taken to minimize the potential bias resulting from these financial associations.⁹¹⁸
 - 3) Retaining all the files containing information regarding the investigators' financial interests for a minimum of two years following the marketing approval.⁹¹⁹

Based on the disclosed information, the FDA may conclude that the financial interests raise concerns for the integrity of the data. In such circumstances, the FDA may issue audits of the investigator's data, request further analyses, request independent studies, or refuse to consider all the data obtained from that clinical study.⁹²⁰ As mentioned below, a study shows that in practice the FDA often does not review such disclosed information.

Notable differences exist between the Israeli COI disclosure provision and the U.S. FDA. Table 7.1 below describes the significant differences between the two regulatory provisions.

Table 7.1: Differences between Israeli and U.S. FDA Regulatory Provisions Addressing Investigator's Financial COI⁹²¹

Regulatory Requirement	Israel	U.S. FDA
Information disclosed	Sponsor-investigator affiliations (business or personal).	Financial arrangements; significant payments; propriety interests; and significant equity interests.
Disclosed by	Trial investigator.	Trial sponsor.
Disclosed to	Helsinki committee as part of the research application form.	FDA as part of the marketing approval process.
Time the information is disclosed	Before the trial begins.	After the trial begins.

⁹¹⁶ Proprietary interest is defined as any property or other financial interest in the product including patent, trademark, copyright or licensing agreement. *Id.* at §54.2(c).

⁹¹⁷ Significant equity interest in the sponsor of a covered study is defined as any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices, or equity interest exceeding 50,000 USD in a publicly traded corporation. *Id.* at §54.2(b).

⁹¹⁸ *Id.* at §54.4(a)(3)(v).

⁹¹⁹ *Id.* at §54.6(b)(1).

⁹²⁰ *Id.* at §54.5(c).

⁹²¹ The Author analysis of the FDA and Israeli COI regulations.

Updating financial disclosed information	Not required.	Investigator must provide updated financial interests information status.
COI decision making authority	The director of the institution. ⁹²²	The FDA.
Consequences for COI decision	Not specified.	Audit the data; additional analyses; request independent studies; or decline the entire data.
Steps taken to minimize COI	Not required.	Sponsor responsibility.

Despite the shared objective to promote valid scientific data portrayed in the two countries' provisions, Table 7.1 shows some notable difference between the provisions. Under the FDA regulations, assessing investigator's financial COI requires detailed information regarding the investigators' financial interests both resulting from the associations with the trial sponsor and from any proprietary interests in the investigational product. The U.S. regulations provide detailed definitions such as what constitutes significant equity interests or proprietary interests which ought to be disclosed. Whereas the Israeli provision for disclosure requires only information regarding the affiliation between sponsor and investigator and does not refer to other types of financial interests.

The other two most prominent differences are the entities to which the information is disclosed, and the responsibility to address identified COI. While the Israeli provision requires the investigator to disclose information to its employer, the medical institution, the FDA provision basically bypasses the host institution and requires the information to run from investigators to sponsors to the FDA.⁹²³ Additionally, in contrary to the U.S., the Israeli provision does not impose any responsibility upon the investigator, or the sponsor for that matter, to take steps to minimize the effects of such COI or to update the status of the information disclosed. Beyond the initial disclosure, investigators are therefore not required to take any additional steps.

⁹²² See the Guidelines for Clinical Trials *supra* note 35 at §9.2.

⁹²³ One of the criticisms in the U.S. argues that bypassing the host institutions disallows these institutions to cross-check the information obtained from the FDA forms, with the information provided by investigators in accordance to the institutions' internal COI processes. For this reason apparently some research institutions in the U.S. require both the sponsors and the investigators to provide copies of all the submitted FDA financial disclosure forms to their IRB. See Barnes & Florencio *supra* note 23.

Moreover, the Israeli provision does not contain any explicit list of actions to be taken by the institution or agency once it determines possible COI based on disclosed information. Such regulatory gaps may create the inconsistencies in the application and interpretation observed among the hospitals in the interview phase. The Israeli provision also does not require the COI decision-making authority to re-review initial or updated information during the course of the trial. As one might argue, imposing non-compliance responsibility on the investigators and sponsors if information is inaccurate or out-of-date as well as imposing measures to mitigating any potential COI, has two potential advantages. First, it could help deter investigators and sponsors from not complying with their regulatory responsibility, as well as make them consistently aware of the severity of the potential risk COI brings. Second, it would provide hospitals with guidance on how to respond to potentially questionable COI situations, enabling the adoption of a consistent policy among hospitals.

On the face of it, the FDA COI disclosure provision with specification for non-compliance sanctions seems to encourage COI awareness and compliance. However, compelling research findings have brought this self-disclosure mechanism into question. A 2009 report issued by the DHHS Office of the Inspector General (OIG) showed that only 1 percent of investigators listed in the financial forms submitted by the sponsor actually disclosed financial interests.⁹²⁴ The report also showed that 42 percent of FDA-approved marketing applications were missing financial information⁹²⁵, while in 31 percent of marketing applications with disclosed financial interests; the FDA did not document a review of such information.⁹²⁶ The OIG thus recommended the FDA take steps to ensure that sponsors submit complete financial information for all clinical investigators, review disclosed financial information, and take action in response to disclosed financial interests.⁹²⁷

⁹²⁴ The OIG report showed that of the 29,691 clinical investigators listed in the financial interests' forms, only 206 disclosed financial interests. See Office of Inspector Gen., Dep't of Health & Human Servs., *The Food & Drug Administration's Oversight of Clinical Investigators' Financial Information*, (January 2009), available at <http://oig.hhs.gov/oei/reports/oei-05-07-00730.pdf> (last visited on Sept. 7, 2012).

⁹²⁵ The report indicates that in 28 percent of these cases the sponsors used due diligence exemption to indicate that they were unable to provide complete financial information. *Id.*

⁹²⁶ *Id.*

⁹²⁷ *Id.*

In Israel, as discussed previously, there are no empirical data analyzing the frequency, extent and/or accuracy of physicians' self-disclosure of affiliations. Cases of nondisclosure rarely receive any public attention, as hospitals are not in the practice of publicizing violations. Two interviewees, however, suggested that occasionally their investigators failed to disclose such information.⁹²⁸ The interview data also indicate that institution officials are not checking the accuracy of the disclosed information. Compliance in disclosure on part of the investigators requires commitment and continuous evaluation by the institution and/or the regulatory agency. It also requires regularly training investigators and institution professionals on the potential risks associated with COI. Krimsky argues that transparency is critical to respond to the effects of COI on ethical conduct, however, he argues that unless transparency results in behavior change, it will not correct the potential research bias and may have a negative impact on public trust.⁹²⁹

It might be in the best interest of the research institutions in Israeli to comply with the disclosure requirements issued by the FDA. Many Israeli hospitals are administrating clinical trials on behalf of sponsors who issue their marketing approval to the FDA. Implications of failing to disclose such financial COI on the part of Israeli investigators might result in the FDA's refusal to allow the investigational product be marketed if the FDA is convinced that the data obtained was unreliable due to the conflicts.⁹³⁰

7.2.2 U.S. NIH Regulations Promoting Objectivity in Research

The U.S. National Institutes of Health (NIH) within the Department of Health and Human Service (DHHS) also issued its regulations designed to advance objectivity in research funded by the Public Health Service (PHS).⁹³¹ These regulations, which were revised in 2011, require research *institutions* to satisfy six key requirements addressing their investigators COI as a precondition to receiving the agency funds:

⁹²⁸ Interview with hospital 4 & 2 officials, at the officials' office at the hospital, Israel (August 31st & September 7th, 2010).

⁹²⁹ See Krimsky *supra* note 807.

⁹³⁰ Based on the 2009 OIG report, the chances the FDA will decline the data due to financial COI might be remote. See Goldner *supra* note 906.

⁹³¹ 42 CFR §50.601.

- 1) Maintaining and enforcing a written policy to respond to the risks of investigator's financial COI.⁹³² These policies must include provisions for monitoring and reporting all investigators' "significant financial interests" funded by the PHS.⁹³³ The regulations require investigators to disclose any "significant financial interest" which could "directly and significantly affect the design, conduct, or reporting of PHS-funded research".⁹³⁴ *Significant financial interest* is broadly defined to encompass almost anything of monetary value and includes:
 - Any investigator remuneration (including salary, consultation fees, honoraria or paid authorship) or value of which exceeding 5,000 USD⁹³⁵;
 - Equity interest of any kind held by investigator (e.g., stock, stock option, or other ownership interest);
 - Investigator intellectual property rights and interests (e.g., patents, copyrights), upon receipt of income related to such rights and interests.⁹³⁶
- 2) Notifying the investigators regarding the institution's COI policy, their disclosure requirements and provide them with recurring COI training.⁹³⁷
- 3) Designating an institutional official⁹³⁸ whose responsibility is to determine whether an investigator's significant financial interest creates financial COI which "could directly and significantly affect the design, conduct, or reporting of the PHS-funded research."⁹³⁹
- 4) Taking necessary actions to manage identified investigator's financial COI. Conditions or restrictions that may be appropriate to employ in managing financial conflicts are discussed in the regulations. These may include inter alia: disclosing the financial COI to the research participants; appointing an independent monitoring committee; modifying the research plan;

⁹³² *Id.* at §50.604.

⁹³³ *Id.*

⁹³⁴ *Id.* §50.603.

⁹³⁵ The definition of significant financial interest was revised in August 2011, lowering the financial disclosure threshold from 10,000 USD in previous regulation to 5,000 USD, as well as lowering the equity interest from 5 percent ownership to any ownership.

⁹³⁶ *Id.* at §50.603. The DHHS regulations however exclude other types of financial interests from investigator's disclosure, including any salary obtained from the institution conducting the research, or income obtained from seminars, teaching, or lectures sponsored by government entities or not-for-profit entities. See *Id.*

⁹³⁷ As noted by the regulations, institutions are required to ensure their investigators acquire COI training every four years, or when they find their investigator not complying with their COI policy or the COI management plan. *Id.* at §50.604(b).

⁹³⁸ *Id.* at §50.604(d).

⁹³⁹ *Id.* at §50.604(f).

disqualifying the conflicted investigator from taking part in the study; or public disclosure of financial conflicts of interest at the time the research data is published or presented.⁹⁴⁰

- 5) Posting on the institution’s website a variety of COI related information. This is part of the revised NIH regulations’ effort to foster more transparency regarding investigator COI. The information to be made publicly available include: institution’s COI policies or any updates thereof; any identified financial COI held by senior or key personnel; and the institution’s written response to individual’s request for their investigator’s significant financial interest.⁹⁴¹
- 6) Reporting to the agency with both initial and updated status regarding the identified financial COI and the COI management plan. As noted by the regulations, these reports should contain sufficient information which allows the agency to understand and assess the appropriateness of the institution's management plan.⁹⁴²

Table 7.2 below describes the main differences between the FDA and the NIH regulations with regard to investigator’s financial COI.

Table 7.2: FDA versus NIH Provisions Addressing Investigator’s Financial COI⁹⁴³

Regulatory Requirement	NIH	FDA
Purpose for financial interest disclosure	To advance objectivity in research funded by the agency.	To ensure the adequacy of the clinical trial data.
Information disclosed	Remuneration exceeding 5,000 USD; equity interest of any kind; Intellectual property rights and interests.	Significant payments paid by sponsor exceeding 25,000 USD; proprietary interest; significant equity interest in the sponsor exceeding 50,000 USD or any equity in non-publicly traded entities.
Disclosed by	Research institution.	Trial sponsor.
Disclosed to	PHS agency, designated institution official. For key officials to the public.	FDA.
In what framework the information is disclosed	As prerequisite for PHS grants or cooperative agreements.	As part of the marketing approval process.

⁹⁴⁰ *Id.* at §50.605(a)(1).

⁹⁴¹ *Id.*

⁹⁴² *Id.* at §50.605(b).

⁹⁴³ Author analysis of NIH and FDA regulations.

Updating financial disclosed information	Investigator must provide updated disclosure of significant financial interests to the institution.	Investigator must provide updated financial interests information status to sponsor.
COI decision making authority	Institutions with PHS oversight.	The FDA.
Consequences for COI decision	COI management plan.	Audit the data; additional analyses; request independent studies; or decline the entire data.
Steps taken to minimize COI	As part of the COI management plan, at the responsibility of the institution.	At the responsibility of the sponsor.

The core purpose shared by both sets of regulations is the demand to respond to financial interests of researchers by virtue of detailed disclosure and COI management. Rather than prohibiting significant financial interests investigators may have, both regulations focus on the responsibility to manage it. Both sets of regulations provide a considerable discretion to the responsible entity for compliance in their COI related decision making, along with reporting to the agency to enable federal oversight. Nevertheless, as Table 7.2 shows, the regulatory approaches differ on several key levels. Seemingly, the two sets of regulations have different policy objectives. The FDA regulation's objective is to maintain the integrity of the research data. Thus, once information is disclosed, the FDA assesses it to maintain whether it had impact on the reliability of the study's data. The FDA usually does not publicize the disclosed financial COI.⁹⁴⁴

However, the overarching objective of the NIH regulations is transparency. Consistent with this objective, the NIH regulations require institutions to post their conflict of interest policies applicable to the agency's funded research on a publicly accessible website.⁹⁴⁵ Institutions are also required to publish all the identified financial COI of their key personnel, including their

⁹⁴⁴ Jennifer A. Henderson & John J. Smith, *Financial Conflict of Interest in Medical Research: Overview and Analysis of Institutional Controls*, Food and Drug L. J. 58, 251 (2003).

⁹⁴⁵ 42 CFR §50.605(a)(5)(i).

name, position, and type and value of the financial interests.⁹⁴⁶ Institutions are required to update this information annually or within 60 days of upon receipt of additional relevant information.⁹⁴⁷

Other notable differences relate to the primary responsible entity for regulatory compliance and the time the disclosed information is mandated. Accordingly, while the NIH regulations place the primary responsibility upon the research institution for identifying and managing possible financial COI of its researchers, the FDA regulations impose the responsibility upon the trial sponsor. Per the FDA regulations, the disclosed information is not shared with the host institutions. Additionally, while the NIH regulations mandate institutions to obtain the financial interest of their investigators at the onset of the trial as a precondition for agency funding, the FDA's required disclosure comes into effect during the course of the trial. Arguably, in case of the FDA regulation, it might be too late to correct any potential inadequacy of data as the data and the trial will have already been conducted.

Although full exploration of the U.S. COI regulations is beyond the scope of this dissertation, it is worth mentioning briefly the wide criticism brought against the lack of standardized objectives and responsibilities under the two most important federal agencies. For example, in 2010 the Secretary's Advisory Committee on Human Research Protections (SACHRP) within the DHHS Office of Human Research Protections called for harmonizing the standards for the reporting, disclosure and review of investigators' financial COI among the federal agencies. In its recommendation the SACHRP argued that bringing together these standards should "...promote industry-academic-public partnerships, allow transparency, ensure fair reporting, promote human subjects protections, and enhance public trust."⁹⁴⁸ Some scholars call the current regulatory landscape a "patchwork" resulting in "...overlapping, incomplete, and occasionally conflicting messages to investigators and institutions involved in collaborative partnerships with industry."⁹⁴⁹ Arguably, the shared federal goals of maintaining the validity of medical research data and the protections for human participants, and the risks to these goals presented by financial COI, creates a compelling argument for consistency in federal regulations.

⁹⁴⁶ *Id.* at §50.605(a)(5)(ii).

⁹⁴⁷ *Id.* at §50.605(a)(5)(iii).

⁹⁴⁸ See the Secretary's Advisory Committee on Human Research Protections (SACHRP) within the Office for Human Research Protections (OHRP) report, March 2010 available <http://www.hhs.gov/ohrp/sachrp/commsec/index.html> (last visited Sept. 7, 2012).

⁹⁴⁹ See Henderson & Smith *supra* note 944.

Considerable discussion with regard to the strengths and weaknesses of each set of regulation would help to foster a thorough and consistent governance framework for the biomedical research arena in the U.S.

7.2.3 Non-government Guidance: the AAMC, AAU and IOM

The federal regulations discussed above are not the only standards pertinent to financial interests of biomedical investigators. Non-governmental and nonprofit entities have issued guidelines to assist research institutions in responding to financial COI in biomedical research. Most prominent are the AAMC-AAU and the IOM. These non-governmental associations essentially propose a more stringent and broader standard than the federal regulations require. Although these professional organizations do not have the power to enforce their guidelines, their recommendations carry a great deal of weight within the medical profession and policymakers in the U.S.

AAMC and AAU Guidance The AAMC and the AAU are nonprofit, non-governmental professional organizations. The AAMC represents all 138 accredited U.S. medical schools and other teaching hospitals and health systems, and the AAU represents 61 leading research universities in the U.S. and Canada. Both organizations provide health and research related policy recommendations and guidance to its member institutions.⁹⁵⁰ In 2008, the AAMC and the AAU issued their guidance report regarding financial COI in medical research intended for academic research institutions.⁹⁵¹ This report called for the adoption of consistent policies and standards for addressing financial COI across academic institutions.⁹⁵² Among their proposals, the AAMC-AAU recommend institutions to feature an analytical framework in which there will be a rebuttable presumption against conflicted investigator participation in research on human subjects. Only “compelling circumstances” will enable researchers to continue involvement in a research project despite the presence of a clear COI. One of the “compelling circumstances” noted is where the best interest of the participants requires such rebuttal.⁹⁵³

⁹⁵⁰ For more information about these professional organizations missions and members, please refer to their website at <https://www.aamc.org/> and <http://www.aau.edu/>.

⁹⁵¹ See the AAMC-AAU report *supra* note 234.

⁹⁵² *Id.*

⁹⁵³ Any approval for rebutting the presumption requires “...particularly stringent analysis of the degree of risk to subjects and of the effectiveness of particular provisions of the conflict management plan to protect subjects and prevent the introduction of bias of the conflicted investigator.” *Id.* at chapter 1(B).

Additionally, the report recommends that the investigators' disclosure of financial interests related to their professional responsibilities should be broadened to eliminate any de minimis threshold. Such disclosure requirements relate to *all* outside financial associations, regardless of whether the individual researcher believes that such associations affect any current or future research.⁹⁵⁴ The AAMC-AAU maintained that extending the disclosure requirements will reduce the failure in compliance with such requirements. As noted in the report, the NIH federal threshold (of 10,000 USD at the time) may be used to define "significant financial interest" triggering the rebuttable presumption against conflicted investigator's participation.⁹⁵⁵

Not only does the report extend the disclosure requirements, it also recommends expanding the scope and the possible audience of reporting the managed COI.⁹⁵⁶ Such extended reporting imposed on institutions includes all researchers, students, and trainees at the institution working on the relevant study; the editors of any publication to which a research manuscript is submitted; substantive public communication⁹⁵⁷ of the research results; and the human subjects of the research project. The report contends that such reporting expansion will ensure broad awareness of potential conflicts and the institutional efforts to address them.⁹⁵⁸

IOM Committee Report The IOM is an independent, nonprofit and non-governmental organization, comprised of distinguish healthcare professionals as well as professionals from other fields such as law, humanities and behavioral sciences. Originally established by the National Academy of Sciences in 1970, the IOM provides advice and analysis to policymakers and the public on important issues in health and health policy.⁹⁵⁹ In 2007, the IOM appointed the Committee on Conflict of Interest in Medical Research, Education, and Practice to evaluate COI in medicine and to propose steps to identify, limit, and manage these conflicts without unconstructively affecting productive collaborations with the biomedical industry. In 2009, the

⁹⁵⁴ *Id.* at chapter 1(C).

⁹⁵⁵ *Id.*

⁹⁵⁶ *Id.* at chapter 1(E).

⁹⁵⁷ This includes any presentation to the media whenever the audience is a "lay person or other professionals". *Id.*

⁹⁵⁸ *Id.*

⁹⁵⁹ Many of the IOM studies are commenced by the U.S. Congress, federal agencies and other non-governmental independent entities. The IOM mission is to serve as a professional adviser to the nation to improve health. For more information about the IOM and its mission, please see IOM website at <http://iom.edu/About-IOM.aspx>.

IOM Committee issued its report which essentially supports certain restrictions on the interactions between researchers and institutions and industry and further fosters disclosure and oversight of certain relations.⁹⁶⁰ The IOM report emphasized the preventive objectives of any COI policies protecting the integrity of professional judgment and maintaining the public trust, rather than trying to correct the bias or mistrust after the fact.⁹⁶¹ The IOM report also stressed that regulations alone may have limited effectiveness when the culture of professionalism promoting professional behavior is lacking.⁹⁶²

Among the IOM report proposals, the report recommended all research institutions adopt, implement and make public their COI policies. It maintained that COI policies are designed to mitigate COI and their impact, and to provide a foundation for public confidence in medical professionals and institutions.⁹⁶³ The report also calls for creating an institutional COI committee, separated from the IRB, charged with managing the identified COI and monitoring compliance with the management plan.⁹⁶⁴ Additionally, the IOM report suggests standardizing content, format, and procedures for disclosure of the financial ties with the industry in view of the current variation in policies among the different institutions.⁹⁶⁵

Moreover, the IOM report recommends comprehensive disclosure of the financial relations between the industry and investigators without minimum threshold, sufficient to allow others to assess their effects on integrity.⁹⁶⁶ In addition, the IOM report suggests that researchers should not conduct research with human participants if they have significant financial interest in an existing or potential product or company which could be affected by the research outcome.⁹⁶⁷ Exception to this general rule is indicated for cases when the COI committee determines that a

⁹⁶⁰ See the IOM report *supra* note 32 at 218.

⁹⁶¹ The IOM report asserts that uncovering bias after the fact might be difficult, time consuming with a great deal of burdensome. Also, a biased judgment can harm the participants, waste resources and damage the research institution involved. See *Id.* at 28.

⁹⁶² *Id.* at Preface at xi-xii.

⁹⁶³ The IOM explains that “physicians retain a high standing with the public compared with the standing of many other professional groups; but physicians should be vigilant because once public confidence is undermined, it may be difficult to restore.” *Id.* at 48-50.

⁹⁶⁴ *Id.* at 88-89.

⁹⁶⁵ The IOM recognizes that by adopting uniform disclosure policies among the intuitions help minimizing the administrative burdens of disclosure. See *Id.* at 90-91.

⁹⁶⁶ This comprehensive disclosure requirement should be made annually and more frequently if the individual’s associations have changed. See *Id.* at 90-91.

⁹⁶⁷ *Id.* at 117-118.

conflicted researcher's involvement is essential for the research⁹⁶⁸; and establishes mechanisms to manage such COI.⁹⁶⁹ The IOM report emphasized that any exception to the rule must be made public.⁹⁷⁰ The report, however, does not provide any details as to what information should be made public.

The IOM report asserts that disclosure of financial associations, though critical; are only the first step in responding to COI.⁹⁷¹ The IOM report further calls for health insurers, accrediting bodies, and government agencies to develop incentives for policy changes promoting transparency in the development of clinical guidelines and accountability in the nature and disclosure of relationships with industry.⁹⁷² Finally, the IOM report advocates investigators conducting clinical research with NIH funding undergo training on COI principles and policies.⁹⁷³

In sum, the non-governmental entities discussed in this sub-section provide more stringent provisions for research institutions on how to identify, assess and manage their conflicted investigators' research activities. These entities are promoting transparency and accountability directed at research institutions through various requirements of broad disclosure, reporting and other mechanisms to enforce their COI policies. Indeed, the academic community has adopted its policies and practices to many of these recommendations.⁹⁷⁴

7.2.4 Policy Recommendation – Investigator COI under the Israeli Regime

As discussed in Chapter 4, the existing Israeli regulatory COI principle requires medical institutions to eliminate COI resulting from investigator's association with the trial sponsor. The definitions and standards, however, for making such COI judgments are unspecified. Thus for example this provision does not define what constitutes COI, nor does it provide clear standards to hospitals on how to eliminate COI once identified. In addition, this regulatory provision

⁹⁶⁸ The example given is a pilot study in which the conflicted investigator is the inventor of an implanted medical device which requires a complex new surgical procedure. See *Id.* at 118.

⁹⁶⁹ *Id.*

⁹⁷⁰ *Id.*

⁹⁷¹ *Id.* at 1-2.

⁹⁷² *Id.* at 236-238.

⁹⁷³ *Id.* at 120.

⁹⁷⁴ See the AAMC-AUU report *supra* note 234.

addresses potential COI resulting from sponsor-investigator affiliations, and is silent to other areas of COI concerns such as an investigator's proprietary interests.

Rather than creating stringent rules and clear standards, Israeli hospitals default to government COI principles for guidance. Substantial variations were found among the interviewed hospital officials with regard to the interpretation and implementation of this COI principle. Variations were found on whether financial affiliation with the sponsor poses a COI risk or not. Variations also found with regard to the affiliations prohibited, the strategies employed once COI is identified, and whether the COI review process would include evaluating equity interests other than sponsor's affiliations.

Such notable variations, as the IOM report warns, may encourage an unhealthy competition among institutions to adopt weak policies and reduce enforcement in order to attract potential sponsors.⁹⁷⁵ It also could help investigators who are eager to avoid any restrictions on their equity pursuit to choose an institution with a weak COI policy.⁹⁷⁶ It may also send a conflicting message to investigators about what financial interests should be prohibited in each institution.⁹⁷⁷ Additionally, the inconsistencies in the implementation of the COI policy may raise concerns about whether scientific validity and participant safeguards are maintained consistently in every institution.

In view of the regulatory gaps, the lack of standardized objectives and responsibilities and the substantial variations in institutional interpretation and implementation, further regulations or guidelines by the government are warranted.⁹⁷⁸ In his interview, the Director-General of the MOH supports adopting a regulatory approach with clear framework for hospitals to work within, leaving little room for variation. There are scarce empirical data and scholarly material on Israeli biomedical research review and approval processes, particularly in the area of COI. In

⁹⁷⁵ *Id.* at 88.

⁹⁷⁶ *Id.*

⁹⁷⁷ Henderson & Smith *supra* note 944.

⁹⁷⁸ The purpose of proposed social regulations is to direct behavior in order to correct the inconsistencies found in the implementation among the hospitals. The theoretical basis for such regulations is the public interest theory of regulations. According to this theory, the policymakers in Israel will need to come to a consensus as to what are the collective goals of protecting against the risks associated with COI, and through such regulations to pursue these goals. For more information about the scope and theories of regulations, see Anthony Ogus, *Regulation: Legal Form & Economic Theory* at 2-4 and 28 (Oxford 2004).

fact, this dissertation apparently is currently the only scholarly source offering empirical data regarding institutional interpretation and implementation of the current regulatory COI provision. In the absence of comprehensive data, any proposed regulations should involve considerable discussion among scholars, scientists, government officials and the public to best foster a thorough and consistent governance framework for COI issues in the biomedical research arena in Israel. A coherent and systematic approach to designing appropriate governance, using risk management and regulations analysis, is imperative.

This dissertation does not intend to suggest that financial interests in research involving human participants are inappropriate, or that those who hold such interests cannot conduct research with scientific objectivity. This dissertation does recognize that any regulations should aim to advance public interest in research in providing them with the adequate information to make informed judgments when assessing the scientific basis of clinical decisions and reporting.⁹⁷⁹ Policy recommendation 1 describe below provides a proposed framework with baseline elements necessary for any regulatory change in this respect.

Policy recommendation 1 The MOH should create a clear framework for identifying, analyzing and managing investigators' financial COI. Such a framework should provide clear definitions and standards in accordance with the following elements:

- a) Defining investigator's COI. What constitutes researchers COI? The scope of the definition should include financial affiliation with the trial sponsor, as well as other equity holdings by the investigators that are dependent on the trial outcome.
- b) Disclosure. What information investigators are required to disclose and when the disclosure is warranted? The regulations may want to adopt disclosure requirements with a de minimis threshold to avoid any misinterpretation by investigators per the recommendation of the AAMC-AAU. Such disclosure should be sufficient to enable the institution to assess the impact of the financial interest on the researcher's professional

⁹⁷⁹ See the AAMC, AAU, the American Council on Education & Association of Public and Land-grant Universities' response to the NIH notice of proposed rulemaking 2010, available <https://www.aamc.org/download/140594/data/081710.pdf> (last visited Sept. 7, 2012).

judgment.⁹⁸⁰ It also needs to address disclosure updates by investigators once their financial status changes during the course of the trial.

- c) Managing COI. What course of actions should institutions take once a potential COI is identified? The provisions should stress that disclosure in itself is not sufficient to protect against the risks associated with COI.⁹⁸¹ As discussed in Chapter 4, several hospital professionals interviewed stated that disclosure in itself is a sufficient tool to address the risks of COI. Thompson warns that disclosure mechanisms can cause ‘deficiency of disclosure’.⁹⁸² Also, the IOM report warns that merely disclosing the information without taking additional steps to eliminate or manage COI, will probably continue to pose risks to objective judgment and weaken the public trust.⁹⁸³

The appropriate actions in managing financial conflicts should be detailed in the regulatory agenda. Similar to the NIH regulations, such proposed actions may include inter alia: disclosing the financial COI to the research participants; appointing an independent monitoring committee; modifying the research plan; disqualifying the conflicted investigator from taking part in the study; or disclosing financial COI at time the research data is published or presented.⁹⁸⁴ The regulations may adopt the rebuttable presumption analytical framework restricting participation as suggested by the AAMC-AAU once significant financial COI is identified, with limited extenuating circumstances.

- d) Investigator training. What mandatory training with regard to COI principles and policies should the investigators conducting clinical research with human participants undergo?

⁹⁸⁰ The IOM recommends that, in order for the disclosure strategy to be effective, it has to include sufficient information, including the nature, scope, duration and monetary value of the affiliation, presented for those who review it. See IOM report *supra* note 32 at 67.

⁹⁸¹ See Krinsky *supra* note 807.

⁹⁸² Such deficiency entails the risk that those who review the disclosed information, particularly trial participants, may not know how to interpret it, or may not have other alternative courses of actions. See Thompson *supra* note 34 at 573-576.

⁹⁸³ The IOM theoretical assumption is that the public trust in a research venture is the building block of its entire formation; without such trust, recruitment, funding and innovation cannot be maintained. See the IOM report *supra* note 32 at 8.

⁹⁸⁴ 42 CFR §50.605(a)(1).

Notably, the existing mandatory regulatory requirement for investigator's 'appropriate training' includes the international Good Clinical Practice (GCP) standards.⁹⁸⁵ These GCP standards do not discussed issues related to COI.⁹⁸⁶

- e) Reporting information to MOH. What COI information should be reported to the MOH for the purposes of regulatory compliance monitoring and oversight? In view of the fundamental regulatory objective to maintain the validity of the data and protection of human participants, once the institution finds financial COI and takes necessary actions to mitigate it, such information should be reported to the MOH for monitoring and oversight. The regulations provide the MOH with extensive authorities of monitoring and oversight through on-site inspections.⁹⁸⁷ Similar to the NIH regulations, the institution's reports should contain sufficient information to allow the MOH to understand and assess the appropriateness of the Institution's COI management plan. The assumption is that consensus among the stakeholders is crucial to avoid any misunderstanding or serves as an excuse for noncompliance. The new regulations should also specify possible remedies available for the MOH for non-compliance. The new regulations should also include specific sanctions for noncompliance with the disclosure requirements directed at investigators, along with the requirement for institutional monitoring.⁹⁸⁸
- f) Communicating disclosed information. What COI related information should be communicated and to what audience? This is part of the objective to foster more transparency in the biomedical arena in Israel. Transparency is essential in determining whether COI policies and practices are reasonable and if they are implemented fairly.⁹⁸⁹ As other scholars believe, governance strategies are essential to ensure that the public perceives researchers as being distanced from private industry and are promoting the public's interest.⁹⁹⁰ Consistent with such objective, the new regulatory provisions should require institutions to post on behalf of their investigators the identified financial COI on

⁹⁸⁵ See the ICH GCP *supra* note 52. Notably, these ICH GCP Guidelines were never explicitly codified in the U.S.

⁹⁸⁶ See discussion in chapter 4 section 4.1.1.

⁹⁸⁷ The Guidelines for Clinical Trials *supra* note 35 at §18.3.

⁹⁸⁸ The AAMC, for example, clarified that any COI policy should consist of well defined possible sanctions for noncompliance for investigators, including dismissal. See the AAMC 2001 report *supra* note 540.

⁹⁸⁹ See the IOM report *supra* note 32 at 58.

⁹⁹⁰ See Caulfield et al. *supra* note 411.

a publicly accessible website. Similar to the NIH regulations, such information should include personnel names, positions, types and values of the financial interests. Institutions should also be required to update this information once the circumstances change. What constitutes “key investigators” should also be clearly defined. Also, one should consider, similar to the AAMC-AAU recommendation, communicating financial COI information related to a specific study with human participants to, inter alia, the following: the research participants, trial funders and all the staff and students working on that research study.

Appendix 2 attached to this dissertation summarizes the abovementioned recommendations to amend the Israeli regime regarding investigator COI derived from the comparative analysis of the U.S. and Israeli provisions.

Section 7.3 below serves to underline existing U.S. regulations, policies and guidance in the attempt to address the COI related challenges found under the Israeli regime with respect to the members of institutional ethics committees and government advisory committees. The comparative component and policy recommendations under this section are based on FDA regulations containing COI screening processes for the members of its advisory committees. The FDA regulations also provide provisions regarding potential COI at the level of institutional ethics committees as well as the AAMC-AAU guidelines. Lastly, this section will conclude with policy recommendation for the Israeli scheme.

7.3 COI at the Research Reviewers’ Level – Comparative Review

As discussed in Chapter 5, the regulatory system, both in the U.S. and Israel, relies on ethics reviewers to safeguard the principles of ethical research. A number of incidents have raised concerns about the ability of these ethics reviews, both as institutional officials and government advisors, to perform their primary objectives in the U.S. and Israel. Among these concerns are the risks of COI resulting from the dual responsibility of serving as an ethics reviewer on one hand and trial investigator on the other. In addition, the relations between the ethics committee members and their peers also causes concerns for COI, as often they are colleagues working for the same institution. The chief challenge for these professionals is finding a way to maintain their

objectivity, while at the same time maintaining the institution's support and fostering the progress and commercialization of new technologies.

In an attempt to address concerns relating to the effects of COI upon the members of ethics committees and/or government advisory committees, the FDA and AAMC-AAU have promulgated regulations and guidelines. Below are the key elements found in these regulations and guidelines.

7.3.1 The FDA Regulations - COI Screening Process for Government Advisory Committees

Federal statutes enacted by Congress formed COI rules applicable to all federal employees, including special Government employees (SGEs) serving on advisory committees. These may include, for example, the Federal Advisory Committee Act (FACA).⁹⁹¹ Specifically in medical research, the FDA has been attempting to balance the need for outside expertise in advisory committees with the risks of COI for several years.⁹⁹²

In the beginning of 2000s the question of the appropriateness of the collaboration between industry and FDA advisors came under increased public scrutiny. The concerns resulted from the high number of outside FDA advisors who were found to have financial ties with the industry they scrutinize.⁹⁹³ This collaboration raises concerns about the potential for bias⁹⁹⁴ and may undermine the public's trust in the review process.⁹⁹⁵ As a result, in 2007, then President George W. Bush signed into law the Food and Drug Administration Amendments Act of 2007⁹⁹⁶ (FDAAA), which established more stringent safeguards applicable to the members of the FDA advisory panels, and required public disclosure of the identified COI on the FDA website.⁹⁹⁷ This

⁹⁹¹ 5 U.S.C. app. 2, §§1 et seq. (2007) which governs advising committee to government agencies. Per this statute, the members of the advisory committee are required "...be fairly balanced in terms of the points of view represented and the functions to be performed by the advisory committee." *Id.* § 5(b)(2).

⁹⁹² See U.S. FDA, Policies and Procedures for Handling Conflicts of Interest with FDA Advisory Committee Members, Consultants, and Experts 2000 available at <http://www.fda.gov/oc/advisory/conflictinterest/policies.html> (last visited Sept. 7, 2012).

⁹⁹³ Studies show that twenty eight percent of FDA advisors who participate on FDA advisory panels have financial or other relations with the industry their review. For more information see Peter Lurie et al. *supra* note 632.

⁹⁹⁴ Lurie et al study showed that seventy three percent of 221 advisory committee meetings between 2001 and 2004 included at least one member with a disclosed financial COI, while only one percent of whom were recused. *Id.*

⁹⁹⁵ Shamoo and Resnik *supra* note 14 at 284-285.

⁹⁹⁶ Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (FDAAA).

⁹⁹⁷ These included recusal of any advisory panel members from taking part in the discussion and voting if they have a financial interest in the particular matter unless they were given a waiver. Also, the new rules requires the FDA to

act also required the FDA to reduce the rate of waivers issued by the agency.⁹⁹⁸ These waivers are granted under certain circumstances, as discussed below, allowing conflicted members to participate in the advisory committee meeting despite their financial COI.

In accordance with the requirements of the FDAAA act and in view of the increased public interest, the FDA issued its revised guidance in 2008⁹⁹⁹ and 2012¹⁰⁰⁰ describing the COI screening process for its advisors, eligibility for participation, waiver procedures and public disclosure guidelines.¹⁰⁰¹ As a general rule, any advisory committee member is prohibited from participating in a committee meeting if he or she or immediate family member has a financial interest, unless a waiver is granted.¹⁰⁰² The process for approving the eligibility of outside members in the FDA advisory committees meeting includes multiple levels of review and assessment. Briefly, the process includes the following reviews and considerations:

- 1) Does the member have a financial interest in the meeting's "particular matters"¹⁰⁰³ which will have "a direct and predictable effect"¹⁰⁰⁴ on his or her financial interests?¹⁰⁰⁵ If no, such member will be able to participate in the meeting.
- 2) If the meeting will have a direct or predictable effect, the FDA will evaluate all financial interests¹⁰⁰⁶ to determine whether they are "disqualifying"¹⁰⁰⁷ for which a waiver will not be considered.

disclose these identified COI or, if applicable, the reasons for granting a waiver. *Id.* at §712(c)(2) and 712(c)(3) respectively.

⁹⁹⁸ *Id.* at §712(c)(2)(C).

⁹⁹⁹ See the FDA, Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees (August 2008) available <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf> (last visited Sept. 7, 2012).

¹⁰⁰⁰ See the FDA, Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers, (March 2012) available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM295372.pdf> (last visited Sept. 7, 2012).

¹⁰⁰¹ See 5 CFR 2640.103(a).

¹⁰⁰² See FDAAA *supra* note 996 at §712 (c)(2)(A).

¹⁰⁰³ Particular matters are defined in the FDA 2008 guidance as matters that "involve deliberation, decision, or action that is focused upon the interests of specific persons, or a discrete and identifiable class of persons." Broad and policy considerations and educational meetings are excluded from "particular matters". See FDA 2008 guidance *supra* note 999.

¹⁰⁰⁴ Direct effect is defined as "close causal link between any decision or action to be taken in the matter and any expected effect of the matter on the financial interest." Predictable effect is defined as when "a real, as opposed to a speculative, possibility that the matter will affect the financial interest." See 5 CFR 2640.103(a)(3)(i),(ii).

¹⁰⁰⁵ *Id.*

¹⁰⁰⁶ Under these circumstances, the member will have to complete an additional financial disclosure form. See the FDA 2008 Guidance *supra* note 999.

- 3) If the member does not have disqualifying personal financial interests, the FDA will further review whether a waiver could be granted. The decision to grant a waiver involves a balancing standard which assesses whether the member's unique ability to contribute to the committee outweighs his or her financial conflicts.¹⁰⁰⁸ Waivers may be granted to outside members (not federal employees) once either two separate standards are met: (a) The need for the member's services outweighs the potential for a conflict of interest created by the financial interest involved;¹⁰⁰⁹ or (b) The individual's services are necessary to afford the committee the "essential expertise." In order to comply with the "essential expertise" test, the FDA should demonstrate in its analysis that "the member provides important expertise that may not be feasibly acquired through alternative means."¹⁰¹⁰
- 4) If the FDA decides that a waiver could be warranted, it will also have to assess whether granting such waiver will be consistent with the target rate caps imposed by the FDAAA.¹⁰¹¹ The FDA may also consider granting participation or waiver with a non-voting authority.¹⁰¹²
- 5) Lastly, the FDA will disclose on its website the type, nature and magnitude of the financial interests of all the members of its advisory committee who received a waiver¹⁰¹³, and the reasons for granting the waiver.¹⁰¹⁴ Such disclosure is warranted

¹⁰⁰⁷ Certain financial interests were determined so significant to deny granting a waiver. Disqualifying financial interests' circumstances are noted in the FDA guidance and include, inter alia, circumstances in which the advisor has financial associations with the sponsor whose application is the particular matter of the meeting. See *Id.* Also considered disqualifying interests are when the combined value of the member's personal financial interests, such as stocks, consultation work and proprietary interests, exceeds 50,000 USD, then a waiver will not be "ordinarily considered". *Id.*

¹⁰⁰⁸ See Ian J. Kellogg, Prescription for a Cure: Does the FDA's Draft Guidance Adequately Manage Advisory Committee Members' Conflicts of Interest? 19 Stan. L. & Pol'y Rev 300 (2008).

¹⁰⁰⁹ *Id.*

¹⁰¹⁰ *Id.* Also see 5 CFR 2640.302 (b) which provides example of the factors to be considered by the FDA in its evaluation process, including the uniqueness of the individual's qualifications; the difficulty in locating a similar qualified member with no disqualifying financial interests etc.

¹⁰¹¹ FDAAA *supra* note 996 at §712(c)(2)(C) imposed reduced cap rates for waivers granted by the FDA. Per this law, by 2012 the FDA is required to reduce the numbers of waivers granted in 2007 by 25 percent.

¹⁰¹² *Id.*

¹⁰¹³ *Id.* at §712(c)(2).

¹⁰¹⁴ *Id.* at §712(c)(3)

before the committee meeting.¹⁰¹⁵ These new reporting requirements aim to foster more transparency and clarity of the waiver process.¹⁰¹⁶

The Israeli COI screening process for the MOH advisory committee members¹⁰¹⁷, discussed in Chapter 5, is similar to the FDA's eligibility process. Both screening processes were aimed to minimize the effects of the risks associated with COI of the government advisors.¹⁰¹⁸ Similar to the FDA, the Israeli process requires the members to disclose their financial interests, while the MOH assesses it to determine whether the financial conflicting interest may have an effect on the matter.¹⁰¹⁹ Both processes impose the COI decision-making authority upon the government agency, and further authorize it to decide whether to grant a waiver or other restrictions as they deem fit. Both regulations use the necessary expertise standard to warrant an exception for participation of a conflicted member.

The notable difference between the two processes are the fact that the Israeli process does not provide a clear definition of what constitutes prohibited COI, nor a possible list of factors to be considered by the MOH when granting a waiver for a conflicted member. Lastly, the Israeli process does not require the MOH to publish their waiver decisions nor information regarding the nature of the conflicted interests of a member who received a waiver.

These strategies are required to ensuring that government advisors are not perceived as influenced by industry. Nevertheless, the need for clear, well defined standards for the COI process in Israel cannot be overstated. To enable the implementation of good public governance, well-defined standards, norms and processes are essential. In addition, readily available arrangements to implement these policies are required.¹⁰²⁰ Lastly, to enhance transparency, like the demand in the U.S. scheme, the Israeli process should entail provisions to allow public scrutiny over the eligibility criteria for government advisors, along with the specific decisions for

¹⁰¹⁵ The information should be posted at least 15 day before the scheduled meeting. *Id.*

¹⁰¹⁶ See the FDA 2012 guidance *supra* note 1000.

¹⁰¹⁷ See the Director General of the Ministry of Health Notice, 14/09 (October 2009) (Isr.), available at http://www.health.gov.il/hozer/mk14_2009.pdf (last visited Sept. 7, 2012).

¹⁰¹⁸ *Id.* at §5.

¹⁰¹⁹ *Id.* at §6.

¹⁰²⁰ See Hirtle *supra* note 524.

providing waivers to a conflicted-advisor. The sub-section 7.3.3 below will provide a proposed framework for policy change to address these elements.

7.3.2 *The AAMC- AAU Guidelines - COI at the Institutional Review Board Level*

Both the U.S. and the Israeli regime employ an institutional review model in which the responsibility for the evaluation and oversight of human subject research falls to the institutional ethics committee within the host institution. In the U.S. they are called Institutional Review Boards (IRBs). Nevertheless, contrary to Israel, in the U.S. these review boards are not necessarily part of a research institution, as there are for-profit independent IRBs operating as a review boards for clients seeking such review.¹⁰²¹ The responsibilities of the IRBs are described in the U.S. federal regulations for the protection of research participants both by the NIH¹⁰²² and the FDA.¹⁰²³

Both U.S. federal agencies' regulations contain the same COI provision with regard to the members of an IRB. Both regulations require IRB members with conflicting interests to recuse themselves from the initial or continuing review of any project to which they have conflicting interests.¹⁰²⁴ Such requirement aims to ensure that conflicting interests will not compromise the safeguards for the trial participants. Nevertheless, as opposed to the detailed definition of researcher COI, these regulations do not offer any definition for COI for the IRB members. Also, contrary to rich and comprehensive empirical data regarding investigators' COI, there is very little research conducted regarding the nature and effect of COI on the members of the IRBs. The only empirical study collected regarding IRBs was released by the Inspector General (OIG) of the DHHS. The OIG initially raised concerns regarding the IRBs member's COI in 1998.¹⁰²⁵ The OIG later revisited its initial concerns in a 2000 report which indicated that there had been no progress in insulating IRBs from conflicts which jeopardize their mission to protect the human participants.¹⁰²⁶ The OIG called on the NIH and the FDA to ensure that the IRBs were

¹⁰²¹ See Foster Riley *supra* note 772.

¹⁰²² 45 CFR §46.

¹⁰²³ 21 CFR §50 & 56.

¹⁰²⁴ 45 CFR §46.107(e) & 21 CFR §50 & 56.107(e).

¹⁰²⁵ See the OIG 1998 report *supra* note 590.

¹⁰²⁶ See the OIG 2000 report *supra* note 591.

segregated from the conflicts compromising their mission. The OIG recommended, inter alia, requiring more presentation of non-scientific and non-affiliated members in the IRBs.¹⁰²⁷

In view of the regulatory requirement for recusal, many research institutions and independent IRBs established policies responding to COI of their IRB members recognizing the risks of such COI to judgment objectivity. Nevertheless, variations in the policies adopted by the various institutions were found. The AAMC-AAU responded to the situation by recommending adopting a clear and comprehensive COI policy to address the possible COI at the IRB level.¹⁰²⁸

Furthermore, they recommended medical institutions compose clear COI policies to address the disclosure and management of COI. Such policy should include at minimum the following:

- a) Provisions for COI disclosure by the IRB members to include *all* financial interests with de minimis threshold, similar to those required from the trial investigators. This disclosure should be updated at least annually. and
- b) Provisions explicitly specifying the procedure of which these COI will be identified and evaluated with a strong recusal strategy.

The U.S. IOM also discussed the significant role of these COI policies stipulating that “Policies designed to reduce COIs and mitigate their impact provide an important foundation for public confidence in medical professionals and institutions.”¹⁰²⁹ In 2002, the IOM report also emphasized the importance of an institutional culture that facilitated ethical behavior by IRB members.¹⁰³⁰ In its conclusion, the IOM report warns that should medical institutions fail to strengthen their internal COI policies, more pressure to impose government regulations will be increased.¹⁰³¹

In sum, compared to the rich and comprehensive research conducted on investigators COI, to date little attention was drawn to COI for the IRB members. While the OIG suggest enhancing compliance and responding to COI through regulatory oversight and procedural changes, the

¹⁰²⁷ *Id.*

¹⁰²⁸ AAMC-AAU 2008 report *supra* note 234.

¹⁰²⁹ IOM report *supra* note 32 at 51.

¹⁰³⁰ See Bowen *supra* note 340 at 556-557.

¹⁰³¹ IOM report *supra* note 32 at 1-4.

non-governmental organizations suggest (at least for medical institutions) adopting comprehensive and clear policies.

7.3.3 Policy Recommendations – COI for the Research Reviewer under the Israeli Regime

Government advisory committee As discussed in Chapter 5, the Israeli regime, much like the U.S. experiences the “shared pool dilemma”, whereby a limited number of scientific experts are in high demand to both the government and industry.¹⁰³² This is especially true in Israel, a small country, where the “pool of experts” is smaller than in other more populated countries. This shared pool dilemma raises the tension between impartiality and competence. In the U.S., this tension was subject to ongoing efforts by the FDA to reduce its advisors’ COI in order to maintain the public confidence in the neutrality of the process.¹⁰³³ Similarly, in Israel the MOH COI Guidelines were aimed at regulating COI among the various government advisors in order to maintain the credibility of the process in the public’s eye. Some variations were found in the interview process with regard to the extent of the relational associations between the advisor and the subject matter under review to merit COI determination. I.e. in addition to familial relations between the advisor and the applicant, it was debated whether other collegial or supervisory associations be considered for evaluating COI circumstances.

Notably, as mentioned elsewhere there are virtually no studies conducted on the functions and the effects of COI on the various government advisors in Israel. No empirical data has been collected on the extent of the associations of government advisors with industry or on the effect of these associations on the function of the various advisory committees. In the absence of such comprehensive data, any proposed framework should necessitate considerable discussion to allow the adoption of effective and sufficient agenda for COI among government advisors. Subsequent to the comparative review of FDA regulations, and the findings discussed in Chapter 5, the following is a proposed framework for policy change to be considered to enhance clarity, consistency and transparency. The following policy recommendation provides core principles to guide policy development with regard to COI at the government advisors level.

¹⁰³² McComas et al. “shared pool” dilemma is described to be based on the two assumptions: the first that there is a limited number of qualified experts exists; and the second that the existing potential or real COI of these experts will result in that member acting in a biased manner. See McComas et al. *supra* note 707.

¹⁰³³ *Id.*

Policy recommendation 2 Revising the current MOH COI screening process for government advisors by providing clear definitions and criteria to address the following:

- a) Defining government advisor COI. What constitutes government advisor COI?
Similar to the investigator’s proposed definition, this definition should address the financial affiliation with the trial sponsor, other personal interests such as equity holding, as well as institutional obligations of the advisor to its employer. This definition should also address the extent of the relational associations, supervisory or collegially, between the advisor and the subject matter under review.

- b) Assessing government advisor COI. What are the specific criteria the MOH should consider when determining when a conflicting interest “is continuous and central to the matter of the opinion” to merit participation recusal? Such information will address the problem of disclosure deficiency as indicated by the MOH official interviewed, by assisting the MOH in interpreting the disclosed information for the purposes of COI determination.¹⁰³⁴ It is imperative for the administrative agencies in charge of balancing interests, to have clear definition as to the goal of such a balancing task as well as the considerations guiding the acting agents.¹⁰³⁵

- c) Criteria for waiver. What are the specific criteria the MOH should consider when evaluating whether to warrant a waiver for a conflicted expert to participate in the discussion or decision-making process despite his or her COI?

- d) Communicating information to the public. What information regarding the warrant of a waiver should become public, and in what medium will it be provided?
In accordance with the U.S. IOM report, transparency is necessary when administrating COI policies.¹⁰³⁶ In order for the public to evaluate whether these policies are reasonable, they should be easily available to them.¹⁰³⁷

¹⁰³⁴ See detailed discussion in chapter 5.

¹⁰³⁵ See Daphne Barak-Erez *supra* note 96 at 217.

¹⁰³⁶ See the IOM report *supra* note 32 at 58.

¹⁰³⁷ *Id.*

Appendix 3 attached to this dissertation summarizes the abovementioned recommendations to amend the Israeli regime regarding government advisor COI derived from the comparative analysis of the U.S. and Israeli provisions.

Helsinki committee As discussed in details in Chapter 5, as oppose to government advisors, the current Israeli regulatory scheme does not regulate potential COI for members of the institutional ethics committees (Helsinki committee). During the interview phase, all interviewees taking part in scientific and ethical review expressed a high level of commitment to safeguarding human participants' safety and health. All interviewees at the institutional level were in agreement that the dual responsibility of investigator-ethics members causes concerns for COI and bias. In these circumstances, hospitals employ a strict COI recusal policy in which the ethics committee members serving as the trial investigators will be prohibited from taking part in the discussion, deliberation and voting. At the institutional level, other levels of potential COI, such as familial or commercial, were not addressed by the hospital officials.

The application of such a narrow interpretation of COI by Israeli hospitals is problematic. It may raise concerns for the effectiveness of hospital oversight and diligence in protecting trial participants. These concerns require further review by the research community and/or the Israeli regulator. Policy recommendation 3 described below provides the necessary framework for addressing COI the Helsinki committee.

Policy recommendation 3 Creating a framework for identifying, analyzing and managing COI at the Helsinki committee level. Such a framework should include the following core elements:

- a) Disclosure requirement and recusal policy for Helsinki committee members with conflicting interests. In view of their role to safeguard human participants, disclosure provisions should include all financial interests by IRB members, similar to those required from the trial investigators. Other relational associations should also be considered per policy recommendation 2 above.
- b) Specifications of the procedures by which COI will be identified and evaluated with a strong recusal strategy.

- c) Reporting to the MOH. Provisions for reporting COI decisions and consequences to the MOH for the purposes of compliance monitoring, similar to the process offered for investigator COI. As mentioned above, the regulatory objective to ensure the validity of data and protection of human participants requires institutions to take actions to mitigate financial COI. The regulations provide the MOH with extensive authority to monitor through on-site inspections.¹⁰³⁸
- d) Posting the institution's COI policy for Helsinki committee members onto the institution's website.

Appendix 4 attached to this dissertation summarizes the abovementioned recommendations to amend the Israeli regime regarding institutional research reviewers COI derived from the comparative analysis of the U.S. and Israeli provisions.

Section 7.4 below serves to underline existing U.S. policies and guidance in the attempt to address the COI related challenges found under the Israeli regime with respect to institutional COI. The comparative component and the proposed framework under this section are based on guidelines and/or recommendation issued by the U.S. government office of the OIG¹⁰³⁹ as well as non-governmental organizations, IOM,¹⁰⁴⁰ and AAMC-AAU¹⁰⁴¹. This section will conclude with policy recommendation for the Israeli scheme.

7.4 Institutional COI – Comparative Review

As noted in the introductory section, contrary to the significant response to COI by investigators and government advisors, the existing U.S. federal regime has not targeted institutional COI.¹⁰⁴² In fact, the U.S. NIH's newly revised regulations deliberately do not address it.¹⁰⁴³ As indicated

¹⁰³⁸ The Guidelines for Clinical Trials *supra* note 35 at §18.3.

¹⁰³⁹ See the OIG 2008 & 2011 reports *supra* note 889.

¹⁰⁴⁰ See the IOM report *supra* note 32 at 216-229.

¹⁰⁴¹ See the AAMC & AAU report *supra* note 234.

¹⁰⁴² Federal anti kickback statute generally applies to unlawful payments made to physicians and medical institutions aimed to influence their health care decisions. The federal anti-kickback law objective is to protect the federal healthcare programs and patients from fraudulent health care decisions. See 42 U.S.C §1320a-7b.

¹⁰⁴³ The original NIH's proposed revised regulations notice from 2009 stipulated that institutional COI is an "area of increasing concern" and included a discussion of whether the new regulations should explicitly address it. See DHHS, Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding is Sought and Responsible Prospective Contractors; Request for Comments, 74 Fed. Reg. 21610 (proposed

by David Korn, the agency was convinced by the research community that it is premature to explicitly address this topic in regulations.¹⁰⁴⁴ Against the backdrop of the regulatory landscape, and with the increasing public and scholarly attention on the topic, the OIG, IOM and AAMC-AAU¹⁰⁴⁵ have issued their reports and guidance on institutional COI. Notably, all these reports recognize that increasing collaborations with industry creates serious institutional COI, which may compel research institutions to “reaffirm their highest values of protecting the integrity of their research, the well being of the human subjects who participate in it, and the trust of the public.”¹⁰⁴⁶ All these reports advocate for further federal government regulations on the subject.

7.4.1 The AAMC- AAU and IOM Committee Guidelines – Institutional COI

AAMC-AAU The AAMC first addressed institutional COI in 2002, when it recognized that an institution’s fiduciary responsibilities competed with its ethical obligations in human participant research.¹⁰⁴⁷ The report suggested institutions: 1) separate their financial and research management responsibilities; 2) establish an institutional COI committee to review and assess conflicts and take steps to manage them.¹⁰⁴⁸ Any COI committee should include at least one non-affiliated member and one senior official who have the sufficient seniority and expertise to evaluate and manage the situation.¹⁰⁴⁹ All committee members should be independent of the direct line of authority from research oversight.

By and large, medical institutions have not consistently implemented these recommendations. In 2008, Ehringhaus et al published a survey indicating that only 38 percent of the responding U.S. medical schools have adopted institutional COI policy applicable to financial interests held at their institutions.¹⁰⁵⁰ A much higher rate, 69 percent, adopted institutional COI policies

May 8, 2009), available at <http://edocket.access.gpo.gov/offcampus.lib.washington.edu/2009/pdf/E9-10666.pdf> (last visited Sept. 7, 2012).

¹⁰⁴⁴ See David Korn *supra* note 397.

¹⁰⁴⁵ See the AAMC & AAU 2008 report *supra* note 234.

¹⁰⁴⁶ *Id.*

¹⁰⁴⁷ See the AAMC, Task Force on Financial Conflicts of Interest in Clinical Research: Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution’s Financial Interests in Human Subjects Research (2002) available http://cnmtl.columbia.edu/projects/rcr/rcr_conflicts/misc/Ref/AAMC_2002CoIReport.pdf (last visited Sept. 7, 2012).

¹⁰⁴⁸ *Id.*

¹⁰⁴⁹ *Id.*

¹⁰⁵⁰ In this survey Ehringhaus et al. conducted a national survey of the deans of 125 accredited allopathic U.S. medical schools administered during 2006. See Ehringhaus et al. *supra* note 893.

applicable to their senior officials, and 81 percent established policies applicable to their ethics committee (IRB) members.¹⁰⁵¹ The institutions did, however, adopt the recommendation and incorporated organizational barriers separating the research responsibility from the investment and technology transfer responsibilities.¹⁰⁵² Another study conducted by the OIG in 2011, reported that 70 of 156 responding NIH grantee institutions have written policies and procedures addressing institutional COI.¹⁰⁵³ The report also maintained that institutions, who had written institutional COI policies and procedures, were more likely to identify institutional COI than those who did not.¹⁰⁵⁴ Lastly, the General Accounting Office (GAO), reviewed several universities policies, inter alia, with regard to institutional COI.¹⁰⁵⁵ The GAO report found considerable variations in these universities' policies and procedures, particularly in the areas of technology transfer¹⁰⁵⁶ and university related startup companies.¹⁰⁵⁷

Partly in response to the fact that the academic medical institutions did not implement their 2002 recommendations, the AAMC joint with the AAU issued another report in 2008.¹⁰⁵⁸ In this report the AAMC-AAU restated the importance of developing and enforcing institutional COI policy as well as creating an objective and reliable institutional COI review process.¹⁰⁵⁹ Generally, the report acknowledged that institutional COI might occur when its financial interests, or its officials acting on its behalf, might affect or reasonably appear to affect institutional processes for the conduct, review, or oversight of human subjects' research.¹⁰⁶⁰ As noted, these might occur when the department chair or institute directors has financial interests which conflict with his or her responsibility for oversight of the institution's research activities.

¹⁰⁵¹ *Id.*

¹⁰⁵² *Id.*

¹⁰⁵³ The OIG 2011 report *supra* note 889.

¹⁰⁵⁴ The OIG 2011 report showed that the most common type of institutional conflict identified by the respondent was the institutions' holding equity in non-publicly held companies. Most used strategy by the institutions to address the institutional COI was disclosure. See *Id.*

¹⁰⁵⁵ See U.S. General Accounting Office, Biomedical Research: HHS Direction Needed to Address Financial Conflicts of Interest (2001), available at <http://www.gao.gov/offcampus.lib.washington.edu/assets/240/233072.pdf> (last visited Sept. 7, 2012). (GAO report).

¹⁰⁵⁶ For example, the report found that two of the five universities reviewed had organizational barriers to separate their technology transfer offices from other research activities. See *Id.*

¹⁰⁵⁷ The report found wide variations in the threshold amount of prohibited equity holdings, ranging from 2 percent of a company's equity at one university to 49 percent at another. See *Id.*

¹⁰⁵⁸ See the AAMC & AAU 2008 report *supra* note 234.

¹⁰⁵⁹ *Id.*

¹⁰⁶⁰ *Id.*

The AAMC-AAU laid down general principles to guide institutions in developing their COI policies:

- 1) “Research and financial decision-making processes and agents must be separated.” The report recognizes that failing to separate these responsibilities will significantly heighten the risks to ethical conduct.¹⁰⁶¹
- 2) Rebuttable presumption against conducting the research at the institution with institutional COI should be pursuant. Such presumption should be rebutted only with compelling circumstances approved by the COI committee followed by conflict management plan.¹⁰⁶² Any decision to rebut the presumption “should be made through a rigorous, codified and transparent institutional COI evaluation process.”¹⁰⁶³
- 3) Institutions should ensure that institutional COI will be consistently addressed throughout the institution.¹⁰⁶⁴

The AAMC-AAU report also set forth procedures for disclosing, reporting and managing institutional COI. The report recommended creating a link between the institutional COI process and the IRB.¹⁰⁶⁵ It also sets a requirement that institutional COI policies should be made available to the public.¹⁰⁶⁶

The 2009 IOM report also addressed institutional COI.¹⁰⁶⁷ The IOM report defined institutional COI as occurring when: “an institution’s own financial interests or those of its senior officials pose risks of undue influence on decisions involving the institution’s primary interests.”¹⁰⁶⁸ The IOM report recognized that there is no institutional officer who will be fully independent from COI at the institutional level.¹⁰⁶⁹ For that reason, the IOM report suggests to include

¹⁰⁶¹ *Id.*

¹⁰⁶² Per the report, assessing the compelling circumstances should be determined on a case by case basis with the special nature of the research, the nature of the financial interest and the degree of the risks to human participants. See *Id.*

¹⁰⁶³ *Id.*

¹⁰⁶⁴ *Id.*

¹⁰⁶⁵ The report acknowledges that in some circumstances the IRB should be notified about the potential institutional COI to enable it to conduct the appropriate risk-benefit ratios, and consider inclusion of disclosing the informed consent process/document. *Id.*

¹⁰⁶⁶ *Id.*

¹⁰⁶⁷ The IOM report *supra* note 32 at 216.

¹⁰⁶⁸ *Id.*

¹⁰⁶⁹ The IOM acknowledged that handling COI at the institutional level is a challenging in terms of obtaining an objective review. As noted, in many circumstances the institutional officer in charge of such review may stand to

independent-non-affiliated members in the committee overseeing COI.¹⁰⁷⁰ The IOM report also called on the institution's board and senior officials to be accountable for ensuring their institution is indeed managing its own interests.¹⁰⁷¹

Similar to the AAMC-AAU report, the IOM report also recommended that the board of trustees or "equivalent governing bodies" within research institutions should establish their own committee to review, monitor and manage institutional COI. This committee should annually report about their activities to the institution's board and make those activities public.¹⁰⁷² Lastly, the IOM report recommended the NIH adopt specific regulations to respond to institutional COI.¹⁰⁷³ The IOM report indicated that by virtue of regulations and further guidance, the NIH can encourage the adequate and consistent implementation of institutional COI policies.

Despite emphasizing the importance of dealing with institutional COI by means of disclosure and management, the IOM report did not propose a well defined framework for how to assess and manage these conflicts.¹⁰⁷⁴ The IOM report did, however, suggest the DHHS execute additional research on COI policies.¹⁰⁷⁵

Despite strong recommendations to voluntarily develop and implement institutional COI policies, institutions have not consistently responded. As mentioned above, only 38 percent of the responding U.S. medical schools have adopted institutional COI policies applicable to financial interests held at their institutions.¹⁰⁷⁶ Fundamental variations were found among institutions who did institute such policies, including variations in the type of transactions prohibited and the implementation policies.¹⁰⁷⁷ Due to these varying responses to institutional

benefit indirectly from the COI, as the institution's financial welfare may be in stake, and thus be reluctant to respond to it. See *Id.* at 225.

¹⁰⁷⁰ *Id.*

¹⁰⁷¹ *Id.* at 228-229.

¹⁰⁷² The report acknowledged that some information should not be made public in order to protect certain confidential personnel information or pending intellectual property. *Id.* at 228.

¹⁰⁷³ *Id.*

¹⁰⁷⁴ See Liang & Mackey *supra* note 595.

¹⁰⁷⁵ See the IOM report *supra* note 32 at 22.

¹⁰⁷⁶ See Ehringhaus et al. *supra* note 893.

¹⁰⁷⁷ For more information regarding the institutional variations in financial COI policies, see Henderson & Smith *supra* note 944.

COI, some scholars regard the current system as fragmented and weak.¹⁰⁷⁸ Per these scholars, the federal agencies have failed to incentivize research institutions to institute effective institutional COI polices through a lack of mandated regulations.¹⁰⁷⁹

In the wake of the emerging data showing inconsistency in institutional COI policies and procedures, and in view of the increasing public and scholarly attention on the topic, the governmental OIG and GAO offices urged for a solution to come at the federal level. In its report, the GAO called the DHHS to advance and communicate “best practices for institutions to identify and manage investigator and institutional financial conflicts of interest”. The GAO also recommended the DHHS to issue guidance or regulations to address institutional financial conflicts of interest, to ensure that research integrity and human participants are adequately protected.¹⁰⁸⁰ Some scholars seem to agree, arguing that the success of adequately responding to institutional COI depends on regulatory incentives promoting widespread adoption of such polices. As argued, these incentives should be achieved through specific federal regulations imposing reporting requirements upon institutions for oversight purposes.¹⁰⁸¹

7.4.2 Policy Recommendations – Institutional COI under the Israeli Regime

As discussed in Chapter 6, Israel has been undergoing a profound transformation of privatization, influenced by the U.S. model, enhancing the competitive research enterprise within public-not-for-profit hospitals. Similar to the U.S. scheme, the Israeli regime has no statutory provisions that directly govern institutional COI despite entrepreneurial opportunities for the hospitals in Israel. Per the Director-General of the MOH, the magnitude of these opportunities is considerably low in value, compared to the U.S., and thus should not merit any regulatory response.¹⁰⁸² Notably, there are no collected data with regard to the type and amount of payments, grants or donations received from the industry, as well as no published information regarding the hospitals’ ownership interests in for-profit corporations, patents and/or the investments made by the senior officials at the institutions. Thus, with lack of such fundamental

¹⁰⁷⁸ See Liang & Mackey *supra* note 595.

¹⁰⁷⁹ *Id.*

¹⁰⁸⁰ See the GAO report *supra* note 1055.

¹⁰⁸¹ See Liang & Mackey *supra* note 595.

¹⁰⁸² Interview with the Director-General of the MOH *supra* note 521.

information is it currently difficult to evaluate the scope of the institutional COI in research institutions in Israel. At a time when the government is actively encouraging not-for-profit government-owned hospitals to financially gain from their new publicly funded discoveries, assessment of its implications is imperative.

Despite the absence of regulatory provisions, the interview phase suggests that some hospitals (three of the seven hospitals sampled) were addressing these conflicts applicable to financial interests held at their institution. Nevertheless, wide inconsistency is found in the measures taken to respond to institutional COI. As the comparative analysis suggests, inconsistencies were also found among research institutions in the U.S. despite governmental and professional trade recommendations and guidance. The literature in the U.S. by and large criticizes such incoherent policy urging research institutions to develop and apply comprehensive institutional COI policies, as well as advocating for federal rules. These proposals will be part of recommendation 4 discussed below.

In addition to lack of regulatory guidance and the wide variations in institutional COI policies found among the hospitals in Israel, the existing regime appears to ensure joint assessment of factors related to ethics and profit. As discussed in Chapter 6, the current regulatory regime requires the representation of the hospital's management within the ethical evaluation of clinical research. The hospital officials interviewed were deeply divided with regard the role management representatives' play, and whether this role creates concerns for bias. Learning from the U.S. experience, recommendation 4 below calls for further review and assessment of organizational framework and infrastructure to address potential institutional COI.

Moreover, in two of the sampled hospitals, the current supervisory structure raises more institutional COI concerns. In these two hospitals, the head of the R&D department is responsible for reviewing and approving technology transfer contracts with the industry, and also reviewing and approving ethical evaluations made by the Helsinki committee. In the U.S. the AAMC-AAU considered these circumstances as concerning practices in view of the risk that the institution's financial interests could affect or reasonably appear to affect the institution's practices, including the conduct, review, or oversight of human research. The AAMC-AAU

warns that a joint ethical and business framework significantly amplifies “...the risks of compromising the safety of human subjects and the integrity of the research performed...”¹⁰⁸³

Recommendation 4 discussed below will propose to revise the Israeli regulations to ensure separating the responsibility for oversight of human participant studies from the responsibility for institutional investment endeavors and technology transfer plans.

Policy recommendation 4 Creating a regulatory framework for identifying, analyzing and managing institution’s COI; *or* alternatively urging research institutions, through mandatory guidelines, to develop and enforce a framework for identifying and assessing institutional COI policies with MOH oversight. The key elements of such a framework should parallel the elements discussed with regard to investigator’s COI. Consistent with recommendation 1, these elements should include definitions, disclosure, and assessment, COI management, reporting and posting requirements. Particularly for institutional COI, the following key provisions should be considered:

- a) Establishing an institutional COI committee. Such an autonomous committee would be in charge of conducting impartial review of the institution’s financial interests and determining whether such interests create concerns for COI in research at the institution. The emphasized requirement is that this separate committee act as an “independent watchdog”, which necessitates its members be autonomous from protecting the institution’s financial security or benefiting from the financial investment they review.¹⁰⁸⁴ Thus, this committee should be separated from the direct line of authority responsible for the ethical evaluations of specific research applications, particularly the Helsinki committee. Per AAMC-AAU recommendation, this committee should be comprised of at least one senior institutional official with sufficient expertise to evaluate the competing interest, as well as one non-affiliated public member.¹⁰⁸⁵

¹⁰⁸³ See the AAMC & AAU report *supra* note 234 at chapter 2 §C(1).

¹⁰⁸⁴ For more information about the possible solutions to institutional COI in research institutions, see Liang & Mackey *supra* note 595; and Barnes & Florencio *supra* note 23.

¹⁰⁸⁵ See the AAMC-AAU 2008 report *supra* note 234.

- b) Organizational structure. Creating sufficient organizational barriers to separate the responsibility for protecting human participants from responsibility for institutional investment endeavors and technology transfer plans.
- c) Defining institutional COI. Proposed adopting the IOM report definition in which institutional conflicts arise when an institution's own financial interests, or that of its senior officials, pose risks of undue influence on decisions involving the institution's primary interests.¹⁰⁸⁶ To evaluate effectively, the institution and its officials' financial interests should be disclosed and updated to a designated institutional office.
- d) Managing institutional COI. Rebuttable presumption policy should be adopted against conducting research involving human participants at the premises of the institution in significant institutional COI circumstances. The AAMC provides a list of circumstances in which such presumption should be applied, including circumstances where the institution is entitled to receive royalties from the sale of the investigational product; or when the institution obtained an equity interest in the trial sponsor company.¹⁰⁸⁷

Per the AAMC recommendations¹⁰⁸⁸, this presumption could be rebutted when the circumstances are compelling and the institutional COI committee approves and establishes an effective conflict management plan. It is proposed that the following criteria, discussed by the AAMC-AAU, be used when assessing compelling circumstances: the nature of the interest; proximity of the interest to the research; the degree of risk to participants; and whether the specific institution is "uniquely qualified" due to its attributes or experience to conduct the research.¹⁰⁸⁹

Appendix 5 attached to this dissertation summarizes the abovementioned recommendations to amend the Israeli regime regarding institutional COI derived from the comparative analysis of the U.S. and Israeli provisions.

7.5 Conclusion

¹⁰⁸⁶ See the IOM report *supra* note 32.

¹⁰⁸⁷ See the AAMC 2002 report *supra* note 1047.

¹⁰⁸⁸ *Id.*

¹⁰⁸⁹ *Id.*

The objective of this Chapter was to draw lessons from the rich experience of U.S. institutions in attending to similar COI challenges faced by the Israeli regime for the purposes of making policy recommendations. The comparative review of the U.S. regime explored parallels the analysis of three areas of potential conflicts discussed in Chapters 4-6: researcher; research reviewer; and institutional. Notably, similar to the U.S., individual investigators and government advisors in Israel are subject to regulatory provisions imposing review and assessment processes designed to eliminate or mitigate against COI. Nevertheless, the members of institutional ethics committee (Helsinki committee) and research institutions were more or less not under the regulatory radar.

This Chapter offers several recommendations for creating an adequate COI framework. The overarching themes of these recommendations are transparency and accountability to enhance scrutiny and uniformity to the Israeli biomedical scheme. The policy recommendations include key elements of COI disclosure requirements applicable to all levels of stakeholders involved in human participant research, as well as clear definitions, standards and structure to identify and evaluate COI circumstances. Any consideration for policy recommendation necessitates considerable discussion among scholars, scientists, government officials and the public to best foster a thorough and consistent governance framework for COI issues in the biomedical research arena in Israel. A coherent and systematic approach to designing appropriate governance, using risk management and regulations analysis is imperative.

CHAPTER 8: Conclusion

“The growing role of governments in regulating conflicts of interest is in part a response to the failure of physicians and scholars to deal adequately with the problem and in part a result of the greater stake that society has in medical practice and research.” [Dennis F. Thompson, *Restoring Responsibility: Ethics in Government, Business and Healthcare*]¹⁰⁹⁰

The global entrepreneurialism of biomedical research and its close ties with the private sector has introduced powerful financial incentives into the public arena. In Israel, through powerful forces of privatization influenced by the U.S. model, the enterprise of competitive research has been enhanced. Israel’s current economic priorities and its regulatory scheme comprised mostly of self-regulated organizational policy have been gradually allowing entrepreneurial incentives within medical research in public institutions to flourish.

Scandals have raised concerns as to whether those in charge of conducting, overseeing and evaluating research uphold a commitment to scientific and ethical standards. In response to public outcry, the government has initiated mechanisms aimed at limiting the potential negative influence of commercial COI through the introduction of disclosure and oversight mechanisms. These mechanisms portray the moral and political characteristic of the regulatory environment in Israel, aiming to enhance elements of accountability and transparency within the realm of medical research.

The question discussed in this study was whether the government-created mechanisms are adequate responses to the influence of commercial incentives and values on the otherwise self-regulated research landscape. Essentially, it concerns how well the risks associated with COI are advocated for and protected in research under the current scheme. For the most part this study suggests that the current safeguards and infrastructure are lacking well-defined standards, norms and processes on how to implement them. Apparently, the current Israeli regime leaves the

¹⁰⁹⁰ Thompson *supra* note 34 at 295-297.

stakeholders in charge of research oversight as well as the public at large with certain fundamental unaddressed issues.

This dissertation does not, however, take the stand that financial interests in research involving human participants are inappropriate; neither does it make assumptions that those who hold such interests cannot conduct research with scientific objectivity. This dissertation does recognize that any regulatory framework should seek to enhance public interest in research providing it with sufficient information to make informed judgments at the time that it assesses the scientific and ethical base of clinical decisions. Increased commercial incentives in public research call for enhanced public scrutiny.

To understand how the current regulatory framework safeguards the risks associated with COI, Chapters 3 provided a comprehensive study of the structure, standards and processes currently in place within Israel's clinical research infrastructure. In accordance with the current regulatory infrastructure for the approval and oversight of clinical trials, medical institutions, particularly the Helsinki Committees, and the MOH play a central role in safeguarding both the rights of human participants and the scientific validity of the research. Specifically, the regulatory mechanism imposes upon the hospitals and the MOH the responsibility to identify and eliminate COI situations arising from the financial or contractual relationships between trial sponsors and investigators. Furthermore, the scheme also imposes a COI screening procedure to determine eligibility of government advisors used by the MOH for scientific and ethical input in the review of new clinical trial applications.

Chapters 4-6 discussed the practical interpretation and implementation of these regulatory mechanisms with respect to the risks of COI. Based on the literature, Chapters 4-6 were divided into three levels of COI affecting the ethical conduct of medical research: the individual investigator level, the level of research reviewer, and the research institution level. Chapters 4-6 reviewed these three areas of potential conflicts based on the previously described key stakeholders' roles and infrastructure.

Chapter 4 explored the tension between the significant latitude clinical investigators enjoy and the entrepreneurial nature of contemporary medical research. Such tension creates concerns for

COI and calls into question whether personal conflicting interests can undermine investigator's ethical and scientific responsibilities. With significant studies published worldwide suggesting that the increasing collaboration with industry has in fact impacted research findings and publications, many concerns regarding the validity and objectivity of industry sponsored biomedical research, as well as legal or ethical concerns for individual researchers' misconduct and bias were raised.

The concerns for financial COI at the investigator level were explicitly addressed by the Israeli regulator by virtue of researcher affiliation disclosure requirements followed by institutional and governmental review processes. Essentially, rather than restricting the commercial funding of research activities and/or other professional activities, the Israeli regulatory scheme chose to ensure continued commercial funding but with oversight. However, these regulatory mechanisms lack essential definitions and standards for making COI judgments. In addition, these provisions only address specific COI circumstances resulting from sponsor-investigator affiliations, and not other areas of COI. Hospitals, as acting institutional oversight parties, default to government COI principles for guidance, rather than create stringent rules and clear standards.

Against this backdrop of unspecified COI principles, it was imperative to interview the stakeholders in charge of the COI review process, particularly hospital officials. Substantial variations were found among the interviewed officials with regard to the interpretation and implementation of this COI principle. These variations found among the officials related to the question of whether financial affiliation with the sponsor poses a COI risk or not. While some hospitals were willing to recognize the financial affiliation with the sponsor as a COI risk, others were not. Variations also existed in what affiliations are prohibited, the strategies employed once COI is identified, and whether the COI review process also include evaluating investigator's proprietary or equity interests. An inverse correlation was found between the scope of the definition of COI due to sponsor-researcher affiliation, and how the hospitals managed it. Namely, the more narrow the definition of COI is the more likely that the institutions will enforce measures to eliminate it.

These notable variations in the implementation of the COI policy among Israeli hospitals may raise concerns as to whether the regulatory objectives of ethical conduct of research are being

employed consistently. It may also create detrimental competition among institutions who may in turn adopt weak policies and reduce enforcement in order to attract potential sponsors. It could further help investigators who are eager to avoid restrictions on their equity pursuits.

As discussed in the first part of Chapter 7, the regulatory gaps, the lack of standardized objectives and responsibilities, and the substantial variations in institutional interpretation and implementation, require further regulations and/or guidelines by the government. A coherent and systematic approach to designing appropriate governance, using risk management and regulations analysis, is imperative. Policy recommendation 1, explored in Chapter 7, provides a proposed framework with baseline elements necessary for any regulatory change to address COI at the investigator level.

Discussed in Chapter 5, are Israeli regulatory model directed at the protection of the primary goals of clinical research by virtue of independent review and oversight mechanisms. Based on the institutional-state review model, the responsibility for the evaluation and oversight of human subject research is mainly bestowed upon the institutional Helsinki Committee and/or the officials at the MOH. As part of the ethical or scientific evaluation, the MOH is assisted by various professional committees and/or experts providing additional input and recommendations.

The emerging entrepreneurial nature of contemporary biomedical research, and the associations between the research reviewers and sponsors, creates several COI issues which challenge the core design of safeguards. The pivotal concern centers on whether the increasing commercial sponsorship and growing financial incentives for reviewers and/or their institutions may have or be perceived to have impact on the reviewers' impartiality. A number of issues have raised concerns about the research reviewers' ability to perform their primary objectives both in the U.S. and Israel. Particularly in Israel, the State Comptroller reported serious ethical and procedural deficiencies with respect to several institutional Helsinki committees. Concerns have arisen as to whether this ethics review system is well-equipped to safeguard the primary goals of human research. Nevertheless, other than the Comptroller report, very little data exist on the processes, procedures and policies of the members of Israel's institutional ethics committees and the government advisory committee - National Ethics Committee.

As further discussed in Chapter 5, the current regulatory framework distinguishes between the different actors involved in the research review process. While the various government advisory committees are governed by specific COI disclosure and management requirements, the institutional ethics reviewers are left to develop their own internal policies on COI related to their members. In addition, the regulatory scheme imposes a requirement to include public participation within the decision-making processes of these research reviewers.

Interviews were conducted with hospital officials, members of the government advisory committee (the National Ethics Committee) and MOH officials in order to understand their policies and practices in response to member COI. All interviewees expressed confidence in the integrity of their committee members. Overall, interviewees agreed that the dual responsibility of investigator-ethics members causes concerns for COI and bias. A conflict avoidance policy is implemented where the reviewer-PI recuses him or herself from the discussion and decision-making process.

Nevertheless, variations were found between institutional reviewers and government advisor reviewers with regard to the scope and definition of COI when other possible interests are involved. Contrary to the inverse correlation found in Chapter 4, the interview data revealed a direct correlation between the scope of the definition of COI and the measures taken to eliminate or manage it.

Within the government advisory committee, some nuanced variations were found in the interview process with regard to the extent of the relational associations between the advisor and the subject matter under review for COI. In addition to familial relations between the advisor and the applicant, it was debated whether other collegial or supervisory associations should be considered for evaluating COI circumstances. Lack of empirical data on the functions and the effects of COI on the various government advisors in Israel, and lack of a sufficient definition of COI and the variations found in this study, suggests the need for considerable discussion on COI among government advisors. Subsequent to the comparative review of FDA regulations discussed in details in Chapter 7, and the findings discussed in Chapter 5, Chapter 7 a further framework for policy change to advance clarity, consistency and transparency with regard to COI at the government advisors level is proposed.

As for the Helsinki committee members, the lack of guidance by the regulatory regime and the arguably narrow implementation of potential COI considered for the recusal policy indicated by the interviewees are problematic. Applying such a narrow interpretation of COI raises concerns for the robustness and effectiveness of institutional diligence in protecting the ethical conduct of research. These concerns require further review and assessment by the research community and/or the Israeli regulator. Policy recommendation 3, described in Chapter 7, provides a proposed framework of baseline elements necessary for addressing COI at the level of the Helsinki committee.

Discussed in Chapter 6, Israel has been undergoing a profound transformation of privatization, influenced by the U.S. model, enhancing the competitive research enterprise within public-not-for-profit hospitals. The regulatory regime formed a “partnership” between the MOH and the hospitals to determine scientific and ethical priorities. Similar to the U.S. scheme, the Israeli regime has no statutory provisions that directly govern institutional COI despite entrepreneurial opportunities for the hospitals in Israel. With the emerging entrepreneurialism of contemporary biomedical research, the current design of safeguards and the designation of stakeholders in charge of enforcing regulations are now being called into question. These new entrepreneurial hybridized hospitals raise concerns for institutional COI by virtue of their position in safeguarding the primary goals of research. The main concern is that potential biases within institutional decision-making practices and processes will jeopardize the health of research subjects, research integrity, and public trust.

Unlike COI at the individual researcher or government advisor levels, the Israeli regime has no statutory provisions that directly govern hospitals’ COI. On the face of it, one can argue that despite the growing entrepreneurial opportunities encouraged by the government, these have not yet matured into institutional COI so as to be recognized by the Israeli scheme as potentially risking the primary objectives of research. This was the perception of the Director-General of the MOH who argued that the magnitude of these commercial opportunities is considerably low in value, compared to the U.S., and thus should not merit any regulatory response. Notably, there are no collected data with regard to the type and amount of payments, grants or donations received from the industry, as well as no published information regarding the hospitals’ ownership interests in for-profit corporations, patents and/or the investments made by the senior

officials at the institutions. Thus, with lack of such fundamental information it is currently difficult to evaluate the scope and development of institutional COI in research institutions in Israel. At a time when the government is actively encouraging not-for-profit government-owned hospitals to financially gain from their new publicly funded discoveries, assessment of its implications is imperative.

Despite the absence of regulatory provisions, the interview phase suggests that some hospitals (three of the seven hospitals sampled) were addressing these conflicts applicable to financial interests held at their institution. Nevertheless, wide inconsistency was found in the measures taken at hospitals to respond to institutional COI. Such inconsistency is questionable. It may provide confusing messages to the public who are left to ponder why some hospitals consider institutional financial interests in the research they conduct risky while others do not. As the comparative analysis discussed in Chapter 7 suggests, such inconsistency in policy was also found among research institutions in the U.S. despite governmental and professional trade recommendations and guidance. The literature in the U.S. by and large criticizes incoherence, urging research institutions to develop and apply comprehensive institutional COI policies, as well as advocating for federal rules. These proposals are part of recommendation 4 discussed in details in Chapter 7.

In addition to lack of regulatory guidance and the wide variations in institutional COI policies found among the hospitals in Israel, the existing regime appears to ensure joint assessment of factors related to ethics and profit. As discussed in Chapter 6, the current regulatory regime requires the representation of the hospital's management within the ethical evaluation of clinical research. The hospital officials interviewed were deeply divided with regard to the role such management representatives play, and whether it creates concerns for bias. Learning from the U.S. experience, recommendation 4 discussed in Chapter 7, calls for further review and assessment of the organizational framework and infrastructure to address potential institutional COI. At minimum, creating hybridized research institutions with powerful financial incentives requires re-assessment of the organizational framework and infrastructure to address the potential institutional COI such an approach. Consequently, recommendation 4 calls for revising the Israeli regulations to ensure separation of the responsibility for oversight of human

participant studies from the responsibility for institutional investment endeavors and technology transfer plans.

Lastly, the overarching objectives of these proposed recommendations discussed in Chapter 7 aim to promote transparency and accountability to enhance scrutiny and uniformity to the Israeli biomedical scheme. Consistent with such objectives, the policy recommendations discussed in Chapter 7 include key elements of COI disclosure applicable to all levels involved in human participants' research, as well as clear definitions, standards and a structural basis for identifying and evaluating COI circumstances. It further emphasized that any consideration for policy recommendation necessitates considerable discussion among scholars, scientists, government officials and the public to best foster a thorough and consistent governance framework for COI issues in the biomedical research arena in Israel.

There is no doubt that ethically conducted research is an essential safeguard of moral and social values, such as protection of the validity of scientific research and the protection of human health and safety. The protection for human participants' health and unbiased research against potential exploitation is and should be regarded as a global concern. There is thus a strong need for solid research, clear thinking and public discourse about this topic. The analysis has at its premise the fact that the protection of human subjects and the preservation of research integrity within the context of medical research must evolve in step with the changing world of innovation and creative technologies. This study takes the stand that it is important to transparently secure legitimate standards and norms not only for the research community, but also for the welfare of the general public and those who contribute to scientific inquiry as clinical trial participants.

BIBLIOGRAPHY

Primary Sources

1. Statutes & Regulations

Israel

Basic Law: Human Dignity and Liberty, 1992, [Constitution]

Director General of the Ministry of Health, Notice 14/09 (2009), available at http://www.health.gov.il/hozer/mk14_2009.pdf

Director General of the Ministry of Health, Notice 3/08 (2008), available at <http://fohs.bgu.ac.il/helsinki/WorldMedicalTrials.pdf>

Director General of the Ministry of Health, The Procedure for Reviewing Contractual Agreements with Ministry of Health Medical Institutions and Clalit Health Services (2010), available at http://www.health.gov.il/download/forms/a3717_mk04_2010.pdf

Director-General of the Ministry of Health, Notice 8/04 (2004), available at http://www.health.gov.il/download/forms/a2537_mk08_04.pdf

Genetic Information Law, 5761-2000, SH No. 1766 p. 62

Health Ordinance, 1940, P.G. 1065

Medical Practitioners Ordinance [Amendment] Law, 5736-1976

Ministry of Health, The procedure of the activity of the National Committee for Clinical Trials in Drugs, procedure no. 19 (2000), available at <http://www.health.gov.il/pages/default.asp?maincat=11&catId=301&PageId=2206>

National Health Insurance Law, 5723-1994 [1995]

Patients' Rights Law, 5756-1996, SH No. 729

Penal Code, 5738-1977

Pharmaceutical Administration of the Ministry of Health, Guidelines for Clinical Trials in Human Subjects, (2006), available at www.health.gov.il/download/pages/guidelinesclinicaltrialshumanEnglish.pdf

Public Health Ordinance, 5701-1940, last revised 5772-2011, SH No. 22901 p. 742

Public Health Regulations (Clinical Studies in Human Subjects), 1980, KT 4189

Public Service (Gifts) Law, 5740-1979

Public Service (Restrictions after Retirement) Law, 5729-1969

State Service (Discipline) Law, 5723-1963 [1963]

The Basic Law: Freedom of Occupation, 1994

The Prohibition of Genetic Intervention (Human Cloning & Genetic Manipulation of Reproductive Cells) Law, 5759-1999, SH 1697 p. 47

Trust Law, 5739-1979

U.S.

Patient Protection and Affordable Care Act of 2010, 42 U.S.C. §1320q-7h (2011)

5 U.S.C. app. §§1-16 et seq. (2011)

21 U.S.C. § 379d-1 (2011)

35 U.S.C. § 200-212 (2011)

42 U.S.C. § 1320a-7b (2011)

5 C.F.R. § 2640.103 (2012)

5 C.F.R. § 2640.302 (b) (2012)

21 C.F.R. § 50 (2012)

21 C.F.R. § 50.1 (2012)

21 C.F.R. § 54.1(b) (2012)

21 C.F.R. § 54.4 (2012)

21 C.F.R. § 54.2 (2012)

21 C.F.R. § 54.5(c) (2012)

21 C.F.R. § 54.6(b)(1) (2012)

21 C.F.R. § 56 (2012)

21 C.F.R. § 56.107(e) (2012)

21 C.F.R. § 312.3(b) (2012)

45 C.F.R. § 46 (2012)

45C.F.R. § 46.107 (2012)

42 C.F.R. § 50.601 (2012)

42 C.F.R. § 50.603 (2012)

42 C.F.R. § 50.604 (2012)

42 C.F.R. § 50.605 (2012)

2. Administrative Guidance

Israel

The Attorney General, Guidance: Preparing Arrangements to Prevent COI in the Public Service, no. 1.555 (June 2006), available

<http://www.justice.gov.il/NR/rdonlyres/85C736FB-F8D3-494D-885E-2F92E392115F/12239/A11555.pdf>

U.S.

Department of Health and Human Services, Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding is Sought and Responsible Prospective Contractors; Request for Comments, 74 Fed. Reg. 21610 (proposed May 8, 2009), available at <http://edocket.access.gpo.gov/offcampus.lib.washington.edu/2009/pdf/E9-10666.pdf>

Food & Drug Administration, Policies and Procedures for Handling Conflicts of Interest with FDA Advisory Committee Members, Consultants, and Experts (2000) available at <http://www.fda.gov/oc/advisory/conflictinterest/policies.html>

Food & Drug Administration, Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees (August 2008), available <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf>

Food & Drug Administration, Sponsor - Investigator - IRB Interrelationship - Information Sheet Guidance for Institutional Review Boards and Clinical Investigators (10.18.10), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126425.htm>

Food & Drug Administration, Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers (March 2012), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM295372.pdf>

3. Israeli Government Protocols & Administrative Decisions

Knesset Labor, Welfare & Health Committee, protocol no. 80 (October 23rd 2006), available at www.aisrael.org/_Uploads/46312006-10-23-02.rtf

Knesset Labor, Welfare & Health Committee, meeting protocol no. 444 (May 26th 2008), available at www.aisrael.org/Uploads/46312006-10-23-02.rtf

The Joint meeting of the State Audit Committee & the Science & Technology Committee., protocol no. 228 (November 7th 2005), available at <http://knesset.gov.il/protocols/data/html/mada/2005-11-07.html>

The Office of the Chief Scientist “Bioplan 2000-2010”, available at http://www.moital.gov.il/NR/old_res/DF7B4140_7C48_41E0_80EB_679E19237999.files/bio-plan.pdf

Knesset Science & Technology Committee, protocol no. 16 (July 11, 2006), available at <http://knesset.gov.il/protocols/data/html/mada/2006-07-11.html>

Israeli Government’s decision No. 4150 (Aug. 9th, 2005), available at <http://www.pmo.gov.il/PMO/Archive/Decisions/2005/08/des4150.htm>

4. Court Cases

Israel

AAM 9449/06 Zazzon v. Jerusalem Municipality, (October 22 2007), Nevo Legal Database (by subscription)

ADCrimA 1397/03 the State of Israel v. Shavess, 59(4) PD 385 [2004]

CA 2781/93 Ali Daaka v. Carmel Hosp., Haifa [1999] Isr.SC 53(4) 526

CA 6983/94 Pachima v. Perez, 51(5) PD 829, 835 [1998]

CA 6983/94 Pachima v. Perez, 51(5) PD 829, 835 [1998]

ClassA (PT)10356-03-11 Lev Orli v. Ziv Medical Center-Zfat (submitted March 6 2011), Nevo Legal Database (by subscription)

CrimA (TA) 7512-04-10 State of Israel v. Figer Arye (March 2 2011), Nevo Legal Database (by subscription)

CrimA 884/80 State of Israel v. Grossman, 36(1) PD 405, 420 [1981]

CrimC (PT) 1424-07-09 State of Israel v. Dov Dicker (December 7 2009), Nevo Legal Database (by subscription)

CrimC (PT) 1424-07-09 State of Israel v. Dov Dicker (December 7 2009), Nevo Legal Database (by subscription)

CrimC (TA) 5848/05 State of Israel v. Oretzki Gidion (March 14 2006), Nevo Legal Database (by subscription)

HCJ 1045/89 Yaakov Daniel v. The Mayor of Kiryat Ata, 44(3) PD 157 [1990]

HCJ 1045/89 Yaakov Daniel v. The Mayor of Kiryat Ata, 44(3) PD 157 [1990]

HCJ 174/54 Shimmel v. Rashut Mosmechet, 9 PD 459, 462 [1955]

HCJ 202/90 I.B.M. v. The Ministry of Justice and others, 45(2) PD 265, 273 [1990]

HCJ 202/90 I.B.M. v. The Ministry of Justice and others, 45(2) PD 265, 273 [1990]

HCJ 244/86 Ravivo v. Ben Tov Yechiel, 42(3) PD 183 [1988]

HCJ 531/79 Siat Halikud in Petach Tikva Municipality v. Petach Tikva Municipality, 34(2) PD 566, 573 [1980]

HCJ 5734/98 Tzadok Azriel and others v. Israel Land Council Subcommittee, 55(5) PD 859, 865 [1999]

HCJ 595/89 Moshe Shimon v. The Supervisor of the Ministry of Interior Southern District, 44(1) PD 409, 414 [1990]

HDJ 279/60 Gil Hall Ltd. v. Yaari, 15 PD 673, 676 [1961]

5. *International Instruments*

International Conference of Harmonization, Good Clinical Practice Guidelines E6(R1) (June 1996), available at <http://www.ich.org/LOB/media/MEDIA482.pdf>

Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Nuremberg, October 1946–April 1949

World Medical Association, Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects (2008), available at www.wma.net/e/policy/b3.htm

Secondary Sources

1. Books

Barak, Aharon, The Prohibition against Conflicts of Interest in COI in the Public Sphere: Law, Culture Ethics, and Politics 36 (Daphne Barak-Ereaz, Doron Navot & Mordechai Kremnitzer, ed. 2009)

Barak-Ereaz, Daphne, Doron navot, Mordechai Kremnitzer Introduction to COI in the Public Sphere: Law, Culture Ethics, and Politics (Daphne Barak-Ereaz, Doron Navot & Mordechai Kremnitzer, ed. 2009)

Beauchamp, Tom L. & James F. Childress, Principles of Biomedical Ethics, 12 (5th ed. 2001)

Bowen, Angela, Models of Institutional Review Board Function in the Oxford Textbook of Clinical Research Ethics, 556 (Emanuel E. at el. ed. Oxford Uni. Press 2008)

Brody, Baruch, the Ethics of Biomedical Research: An International Perspective (Oxford 1998)

Cox, Neetika Prabhakar et al., Conflicts between Commercial and Scientific Roles in Academic Health Research, in Trust & Integrity in Biomedical Research: The Case of Financial Conflicts of Interest 41 (Thomas H. Murray & Josephine Johnston eds.2010)

Creswell, John W., Research Design: Qualitative, Quantitative and Mixed Methods Approaches (2nd ed. 2003)

Emanuel, EJ. & D. Thompson, the Concept of Conflicts of interest in Medical Research: Historical developments in the Oxford Textbook of Clinical Research Ethics, 760 (Emanuel E. at el. ed. Oxford 2008)

Etzkowitz, Henry, From Conflict to Confluence of Interest: The Coevolution of Academic Entrepreneurship & Intellectual Property Rights, in Trust & Integrity in Biomedical Research 74-75 (Thomas H. Murray & Josephine Johnston ed. 2010)

Feldman, Yuval, the Psychology of Conflicts of Interest in Service in COI in the Public Sphere: Law, Culture Ethics, and Politics 67 (Daphne Barak-Ereaz, Doron Navot & Mordechai Kremnitzer, ed. 2009)

Ferris, L. & D. Naylor, Promoting Integrity in Industry-Sponsored Clinical Drug Trials: Conflict of Interest for Canadian Academic Health Sciences Centers in Law & Ethics in Biomedical Research: Regulations, Conflict of Interest, and Liability 95 (Trodu Lemmens & D. Waring ed. Uni. of Toronto 2006)

Fisher, Jill A., Medical Research for Hire: The Political Economy of Pharmaceutical Clinical Trials (Gutgers 2009)

Glass, Kathleen Cranley, Questions & Challenges in the Governance of Research Involving Humans: A Canadian Perspective in Law & Ethics in Biomedical Research: Regulations,

- Conflict of Interest, and Liability 38 (Trudo Lemmens & D. Waring ed. Uni. of Toronto 2006)
- Hacohen, Aviad, The Prohibition against Conflict of Interest in Jewish Law in Conflict of Interest in the Public Sphere: Law, Culture Ethics, and Politics 127 (Daphne Barak-Erez, Doron Navot & Mordechai Kremnitzer, ed. 2009)
- Hampson, Lindsay A. et al., Empirical Data on Conflict of Interest, in the Oxford Textbook of Clinical Research Ethics, 676 (Emanuel et al. ed. Oxford 2008)
- Institute of Medicine Committee on Assessing the System for Protecting Human Research Participants, Responsible Research: A systems Approach to Protecting Research Participants (Daniel D Federman, Kathi E Hanna & Laura Lyman Rodriguez ed.), National Academies Press (2003)
- Jacobsen, Thomas M. et al., Modern Pharmaceutical Industry: A Primer (2010)
- Johnston, Josephine, Financial Conflicts of Interest in Biomedical Research, in Trust & Integrity in Biomedical Research 11 (Thomas H. Murray & Josephine Johnston ed. 2010)
- Karlberg, Johan PE and Marjorie A. Speers ed., Reviewing Clinical Trials: A Guide for the Ethics Committee (2010)
- Krimsky, Sheldon, The Ethical and Legal Foundations of Scientific Conflict of Interest in Law & Ethics in Biomedical Research: Regulation, Conflict of Interest & Liability, 66 (Trudo Lemmens & Duff R. Waring ed. Uni. of Toronto 2006)
- Lemmens, Trudo, Conflict of Interest in Medical Research: Historical developments in The Oxford Textbook of Clinical Research Ethics, 747 (Emanuel E. et al. ed. Oxford 2008)
- Marien, Michael, Managing Conflict of Interest in the Public Service: OECD Guidelines and Country Experiences (Future Survey 2005)
- Molinoff, Perry, Conflict of Interest in American Universities in the Penn Center Guide to Bioethics 282 (Verdit Ravitsky, Autum Fiester & Arthur L. Caplan ed. 2009)
- Moore, Don A. et al. ed., Conflict of interest: Challenges & Solutions in Business, Law, Medicine, and Public Policy (Cambridge 2005)
- Ogus, Anthony, Regulation: Legal Form & Economic Theory (Oxford 2004)
- Rodwin, Marc A., Conflicts of Interest & the Future of Medicine (Oxford 2011)
- Senor, Dan & Saul Singer, Start-up Nation: The Story of Israel's Economic Miracle (2009)
- Shamoo, Adil E. & David B. Resnik, Responsible Conduct of Research (2003)
- Shelly, Merry, Frankenstein, Penguin Book Ltd. (1992)
- Speers, Marjorie A., Evaluating the Effectiveness of Institutional Review Boards in The Oxford Textbook of Clinical Research Ethics, 560 (Emanuel E. et al. ed. Oxford 2008)
- The Human Radiation Experiments, the final report of the Advisory Committee on Human Radiation Experiments (Oxford 1996)
- Thompson, Dennis F., Restoring Responsibility: Ethics in Government, Business & Healthcare (Cambridge 2005)

Wade, William R. & Christopher F. Forsyth, *Administrative Law* (8th ed. 2000)

Zamir, Itzhak, *Conflict of Interest in Public Service in Jewish Law in the Public Sphere: Law, Culture Ethics, and Politics* 232 (Daphne Barak-Erez, Doron Navot & Mordechai Kremnitzer, ed. 2009)

2. *Administrative & Professional Organization Reports*

Israel

Bilig, Hannah, *Pharmaceutical Administration, Ministry of Health, Clinical Trials in Israel* (no date), available at http://www.health.gov.il/Download/pages/nisoim_kliniim.doc

Inter-ministerial Steering Committee, *Regularization of the Intellectual Property in the Government Offices* (Dec. 2005), available at <http://www.ag.mof.gov.il/NR/rdonlyres>

Israel Life Science Industry website profile report, *The Israeli Life Science Industry: 2001-2010 report: A Decade of Growth*, available at http://www.ilsa.org.il/industry_profile.asp

Israel Medical Association, *Code of Ethics* (2009), available at <http://www.ima.org.il/MainSite/ViewCategory.aspx?CategoryId=3676>

Levy, Shelli, *A Report on Donation in Areas of Health: part of the New Arrangement Bill for 2011-2012*, submitted to the Labor, Welfare & Health Committee in the Knesset (2010), available at <http://www.knesset.gov.il/mmm/data/pdf/m02689.pdf>

Ministry of Health Committee for Contracts with Commercial Companies, *Medical Research Conducted by Investigators during 2009 Compared to 2006-2009 (In NIS)*, (September 6, 2010) (unpublished report) (on file with Author)

Ministry of Health Committee for Contracts with Commercial Companies, *Commercial Companies Investments during the years 2006-2009 in Clinical Trials*, (no date unpublished report) (on file with Author).

Ministry of Health report, *Hospital Institutions & Short-term Hospitalizations in Israel* (2009), available at http://www.old.health.gov.il/Download/pages/mossadot_2009.pdf

Ministry of Health report, *information on Hospitalization Institutions in Israel* (2008), available at <http://www.health.gov.il/pages/default.asp?maincat=1&catId=98&PageId=709>

Ministry of Health, *Hospital Beds & Licensed Work-Stations* (2010), available at http://www.old.health.gov.il/Download/pages/Beds_jan_2010.pdf

Ministry of Health, *medical institutions statistics report* (2008), available at <http://www.health.gov.il/pages/default.asp?maincat=2&catid=514&pageid=4942>

Ministry of Health, *Number of New Clinical Trial Applications in Drugs and non Drugs/Medical Devices 2008-2009*, (2010) (unpublished report) (on file with Author)

Ministry of Industry, Trade and Labor's Foreign Trade Administration *Investment Promotion Center report* (2006), available at www.investinisrael.gov.il

Roman, Ron, Department of Justice, Press Release (Feb. 10 2011), available at <http://www.justice.gov.il/NR/rdonlyres/68CA90B2-EBE3-43E5-85C4-AD99E81EC387/25950/SgiratTik.doc>

The Israeli State Comptroller's Report 55 (2004), available on <http://www.mevaker.gov.il/serve/contentTree.asp?bookid=426&id=2&contentid=7933&parentid=undefined&bctype=7932&sw=1280&hw=954>

U.S.

Association of American Medical Colleges, Protecting Subjects, Preserving Trust, Promoting Progress: Policy & Guidelines for the Oversight of Individual Financial Interests in Human Subjects' Research, (Washington D.C. 2001)

Association of American Medical Colleges, Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research (2002) available http://ccnmtl.columbia.edu/projects/rcr/rcr_conflicts/misc/Ref/AAMC_2002CoIReport.pdf

Association of American Medical Colleges, Protecting Patients, Preserving Integrity, Advancing Health: Accelerating the Implementation of COI Policies in Human Subjects Research (FEB. 28, 2008)

Association of American Medical Colleges et al., Response to the NIH notice of proposed rulemaking 2010, available <https://www.aamc.org/download/140594/data/081710.pdf.pdf>

Department of Health, Education & Welfare, Public Health Services, Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel Charge III, (1973), available at biotech.law.lsu.edu/cphl/history/reports/tuskegee/tuskegee.htm

Eastern Research Group, commissioned report by the FDA, Measuring Conflict of Interest and Expertise on FDA Advisory Committees (2007), available at <http://www.fda.gov/oc/advisory/ERGCoiReport.pdf>

Food and Drug Administration, Notice to Dr. James Wilson, Initiation of Disqualification Proceeding and Opportunity to Explain, University of Pennsylvania Institute for Human Gene Therapy (2000), available at <http://www.fda.gov/foi/nidpoe/n121.pdf>

General Accounting Office, Biomedical Research: HHS Direction Needed to Address Financial Conflicts of Interest (2001), available at <http://www.gao.gov/offcampus.lib.washington.edu/assets/240/233072.pdf>

Institute of Medicine, Conflict of Interest in Medical Research, Education & Practice (Bernard M. Lo & Marilyn J. Field eds., 2009)

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Institutional Review Boards: Report and Recommendation, 43 Fed. Reg. 56,186 (November 30, 1978)

Neal Masia, the Cost of Developing a New Drug: New Wonder Medicines Come from Years of Research, High Costs (April 2008), available at <http://www.america.gov/st/econ-english/2008/April/20080429230904myleen0.5233981.html>

- Office for Human Research Protection (OHRP) report (March 2010), available <http://www.hhs.gov/ohrp/sachrp/commsec/index.html>
- Office of Inspector General, Department of Health and Human Services, Institutional Review Boards: A Time for Reform (1998), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf>
- Office of Inspector General, Department of Health and Human Services, Protecting Research Subject: Status of Recommendation (April 2000), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf>
- Office of Inspector General, Department of Health and Human Services, National Institute of Health: Conflict of Interest in Extramural Research (January 2008), available at <http://oig.hhs.gov/oei/reports/oei-03-06-00460.pdf>
- Office of Inspector General, Department of Health and Human Services, The Food & Drug Administration's Oversight of Clinical Investigators' Financial Information, (January 2009), available at <http://oig.hhs.gov/oei/reports/oei-05-07-00730.pdf>
- Office of Inspector General, Department of Health and Human Services, OEI-03-09-00480, Institutional Conflicts of Interest at NIH Grantees (2011), available at <http://oig.hhs.gov/oei/reports/oei-03-09-00480.pdf>
- Office of Inspector General, Department of Health and Human Services, National Institute of Health, Institutional Conflict of Interest at NIH Grantees (January 2011), available at <http://oig.hhs.gov/oei/reports/oei-03-09-00480.asp>
- The Secretary's Advisory Committee on Human Research Protections (SACHRP) of the Office for Human Research Protections (OHRP) report (March 2010), available <http://www.hhs.gov/ohrp/sachrp/commsec/index.html>

International

- Kakaflikas, Christina, Israel Investment Attraction Program, Report to Economic Development Committee (2011), available at <http://www.markham.ca/markham/ccbs/indexfile/Agendas/2011/Development%20Services/pl110308/Israel%20Investment%20Attraction%20March%208%202011.pdf>
- King, L.W., Translation of the Code of Hammurabi, by the Avalon Project at Yale Law School, available at <http://avalon.law.yale.edu/ancient/hamframe.asp>
- Organization for Economic CO-Operation & Development, Turning Science into Business: Patenting & Licensing at Public Research Organizations, Paris, France, Organization for Economic Co-Operation and Development (2003)
- Organization for Economic CO-Operation & Development, OECD Science, Technology & Industry Outlook (2010), available at http://dx.doi.org/10.1787/sti_outlook-2010-en
- Organization for Economic CO-Operation & Development, Health Data Report (2011), available at http://www.oecd.org/document/16/0,3343,en_2649_34631_2085200_1_1_1_1,00.html

Rosen, Bruce et al., World Health Organization, the European Observatory on Health Care Systems, Health Care Systems in Transition: Israel (Sarah Thompson & Elias Mossialos eds. 2003)

3. Periodicals/Articles

Israel

Barak-Erez, Daphne, Civil Right & Privatization in Israel Yearbook on Human Rights, 205 Kluwer Law International (1999)

Barak-Erez, Daphne, The Annual Book of the Israeli Law, 1992-1993 223 (Israel Bar-Tel-Aviv District 1994)

Chinitz, D., Israel's Health Policy Breakthrough: The Politics of Reform & the Reform of the Politics, Journal of health Politics, Policy & Law 20 (1995)

Flic, Dani, The Health Business Under Neo-Liberalism: The Israeli Case, 25 Critical Soc. Pol'y 180 (2005)

Flic, Dani, The Privatization of the Health Care System and its Commercialization (2007), available at <http://www.ynet.co.il/Ext/Comp/ArticleLayout/CdaArticlePrintPreview/1,2506,L-3372021,00.html>

Glick, Simon, Medical Experimentation on Humans, Asia: articles, summaries and reports of Halacha and Medicine 16 (3-4): 66-73, (1998), available at <http://www.daat.ac.il/daat/kitveyet/assia/nisuyim-2.htm>

Goldblat, Moshe, Patients' Right to Adequate Disclosure (2006) available at http://www.israelbar.org.il/article_inner.asp?pgId=33126&catId=287

Hochman, L., A. Caspi, W. Blasi & V. Charlon, Conducting Clinical Trials in Israel Sponsors find a diverse population, good medical facilities, GCP-compliant investigators, and efficient regulatory processes in Israel, Applied Clinical Trials vol. 10 63 (2001)

Horev, Tovia & Yair M. Babad, Healthcare Reform Implementation: Stakeholders and their Roles—the Israeli Experience, Health Policy 71 (2005)

Koren, Ahuva, Benefits of Conducting Clinical Trials in Israel for Multinational Life Science Companies. J. Biolaw & Bus., Vol. 10, No. 1, 2007

Reches, Avinoam, Introduction in Israeli Medical Association: The Ethical Department and Legal Department, Clinical Trials, at 3-4 (2006) (Isr.), available at http://ima.org.il/ima/FormStorage/Type1/clinical_research.pdf

Shalev, C., Reclaiming the patient's voice and spirit in dying: an insight from Israel, Bioethics 24(3) 134-144 (2010)

U.S.

Anderlik, Mary R. and Nanette Elster, Lawsuits Against IRBs: Accountability or Incongruity? 29 J.L. Med. & Ethics 220 (2001)

- Anderson, Martinson & De Vries, *Nature: International Weekly Journal of Science*, 435 Issue 7043, 737 (2005)
- Angell, Marcia, *Drug Companies & Doctors: A Story of Corruption*, N.Y. Rev. Books, Jan. 15, 2009, available at <http://www.nybooks.com/articles/archives/2009/jan/15/drug-companies-doctors-a-story-of-corruption/>
- Barnes, Mark & Patrik S. Florencio, *Symposium: New Directions in Human Subject Research: Looking Beyond the Academic Medical Center: Investigator, IRB and Institutional Financial Conflicts of Interest in Human-Subjects Research: Past, Present and Future*, 32 *Seton Hall L. Rev.* 525 (2002)
- Bekelman, Justin E. et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A systematic Review*, *JAMA* 454 (2003)
- Blumenthal, David, *Academic-Industrial Relationships in the Life Sciences*, *N. Engl. J. Med.* 349, 2452-2459 (2003)
- Blumenthal, David, *Conflict of Interest in Biomedical Research Biotech in Northeast Ohio Conference: Current Plans and Visions for the Future*, *Health matrix* 12(2): 377-92 (2002)
- Boozang, Kathleen M., Carl H. Coleman & Kate Greenwood, *An Argument Against Embedding Conflicts of Interest Disclosures in Informed Consent*, Vol. 4, No. 3, *J. Health & Life Sci. L.* (2011)
- Bouchard, Ron, *Balancing Public and Private Interests In The Commercialization of Publicly Funded Medical Research: Is There a Role For Compulsory Government Royalty Fee?* 13 *B.U.J. SCI. & TECH. L.* 120 (2007)
- Bozeman, Barry & Daniel Sarewitz, *Public Values and Public Failure in U.S. Science Policy*, *Science & Public Policy* 32, no. 2 (2005), 119-136
- Bozeman, Barry, *Technology Transfer & Public Policy: A Review of Research & Theory*, 29 *Research Policy* 627 (2000)
- Brennan, Troyen A. et al., *Health Industry Practices that Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers*, 295 *JAMA* 429 (2006)
- Caulfield, T. , E. Einsiedel, JF. Merz & D. Nicol, *Trust, Patents and Public Perceptions: the Governance of Controversial Biotechnology Research*, *Nature biotechnology* 24, 11 (2006)
- Coleman, C.H., *Duties to subjects in Clinical Research*, 58 *Vand. L. Rev.* 387 (2005).
- Du Val, Gordon, *Research Ethics: Institutional Conflicts of Interest: Protecting Human Subjects, Scientific Integrity, And Institutional Accountability*, 32 *J. L. Med. & Ethics* 613 (2004)
- Ehringhaus, Susan H. et al., *Responses of Medical Schools to Institutional Conflicts of Interest*, 299 *JAMA* 665, 665 (2008)
- Elliott, Carl & Roberto Abadie, *Exploiting a Research Underclass in Phase 1 Clinical Trials*, 358 *New Eng. J. Med.* 2316 (2008)

- Emanuel, Ezekiel J. et al, Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals, 141 *Annals Internal Med.* 141(4): 282-91 (2004)
- Epstein, Richard A., How Conflict-of-Interest Rules Endanger Medical Progress and Cures, Manhattan Institute for Policy Research (2010) available at http://www.manhattan-institute.org/html/fda_03.htm
- Foster Riley, Margaret, the Future of Regulation: Federal Funding and the Institutional Evolution of Federal Regulation of Biomedical Research, *Harv. L. & Pol'y Rev.* 265 (2011)
- Friedrichsa, Jörg & Friendrich Kratochwil, On Acting and Knowing: How Pragmatism Can Advance International Relations Research and Methodology, *International Organization* 63, 701–31 (2009)
- Gatter, Robert, Conflicts of Interest in International Human Drug Research and the Insufficiency of International Protection, 32 *Am. J. L. & Med.* 351 (2006)
- Gelsinger, Paul & Adil E. Shamoo, Eight Years After Jesse's Death, Are Human Research Subjects Any Safer? The Hastings Center report, 38(2): 25-7 (2008)
- Gilman, Stuart C., Joshua Joseph & Cheryl L. Raven, Conflict of Interest: Balancing Appearances, Intentions and Values, (Ethics Resource Center 2002) available at <http://www.ethics.org/resource/conflicts-interest-balancing-appearances-intentions-and-values>
- Goldner, Jesse A., Childress Lecture: Regulating Conflict of Interest in Research: The Paper Tiger Need Real Teeth, 53 *St. Louis L.J.* 1211 (2009)
- Groeger, Jeffery & Mark Branec, Conflict of Interest in Human Subjects Research, *Critical Care Medicine* 31 (3 Suppl): S137-42 (2003)
- Helmholz, R.H., Money and Judges in the Law of the Medieval Church, 8 *U Chi L Sch Roundtable* 309 (2001)
- Henderson, Jennifer A. & John J. Smith, Financial Conflict of Interest in Medical Research: Overview and Analysis of Institutional Controls, *Food and Drug L. J.* 58, 251 (2003)
- Hirtle, Marie, The Governance of Research Involving Human Participants in Canada, 11 *Health L.J.* 137 (2003)
- Hoffman, Sharona & Jessica Wilen Berg, The Suitability of IRB Liability, 67 *U. Pitt. L. Rev.* 365 (2005)
- Johns, MM., M. Barnes, PS. Florencio, Restoring Balance to Industry-Academia Relationships in an Era of Institutional Financial Conflicts of Interest Promoting Research While Maintaining Trust, *JAMA* 289(6), 741-746 (2003)
- Kaplan, Yehiel S., The Right of a Minor in Israel to Participate in the Decision-Making Process Concerning His or Her Medical Treatment, 25 *Fordham Int'l L.J.* 1085 (2002)
- Kellogg, Ian J., Prescription for a Cure: Does the FDA's Draft Guidance Adequately Manage Advisory Committee Members' Conflicts of Interest? 19 *Stan. L. & Pol'y Rev* 300 (2008)
- Korn, David, M.D., Financial Conflicts of Interest in Academic Medicine: Whence They Came, Where They Went, 8 *Ind. Health L. Rev.* 1 (2010)

- Krimsky, Sheldon, *Academic Integrity: Combating the Funding Effect in Science: What's Beyond Transparency?* 21 *Stan. L. & Pol'y Rev* 81 (2010)
- Krzyzanowska, Rose & Joffe, *Relationships Between Authorship Contributions and Author's Industry Financial Ties Among Oncology Clinical Trials*, *Journal of Clinical Oncology*, 28, 8, 1316-1321 (2010)
- Kubiak Cinead R., *Conflicting Interests & Conflicting Laws: Re-Aligning the Purpose and Practice of Research Ethics Committees*, 30 *Brooklyn J. Int'l L.* 759 (2005)
- Liang, Bryan A. & Tim Mackey, *Confronting Conflict: Addressing Institutional Conflict of Interest in Academic Medical Centers*, 36 *Am. J. L. and Med.* 136 (2010)
- Lowenstein, George, Sunita Sah & Daylian M. Cain, *The Unintended Consequences of Conflict of Interest Disclosure*, *JAMA* 307(7) 669 (2012)
- Lurie, Peter et al., *Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, *JAMA*. 2006; 295(16):1921-1928
- McComas, Katherine A., Leah Simone Tuite & Linda Ann Sherman, *Conflicted scientists: the "shared pool" dilemma of scientific advisory committees*, *Public Understand. Sci.* 14, 285–303 (2005)
- Okike Kanu et al., *Accuracy of Conflict-of-Interest Disclosures Reported by Physicians*, 361 *New Eng. J. Med.* 1466 (2009)
- Peipert JF, *The economic value of medical research: is it worth the investment?* *Obstet. Gynecol.* 99(5 Pt 1):835-40 (2002)
- Ridker, Paul M. & Jose Torres, *Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations: 2000-2005*, *JAMA*. 2006; 295(19): 2270-2274
- Rothman, K., *the Ethics of Research Sponsorship*, *J Clin. Epidemiol.* 44 (Suppl. I) s25, s26 (1991)
- Schatz, Gerald, *Are the Rationale and Regulatory System for Protecting Human Subjects of Biomedical and Behavioral Research Obsolete and Unworkable, or Ethically Important and Inconvenient and Inadequately Enforced?*, 20 *J. Contemp. Health L. & Pol'y* 1 (2003-2004)
- Thompson, Dennis F., *Understanding Financial Conflicts of Interest*, *N. Engl. J. of Med.* 329, 573-576 (1993)

4. *Israeli News Reports*

- Linder-Gantz, Roni, *Hamerkazing Harefuieem Hervichu 282 Million NIH Memechkar Clini Be 2010 (The Medical Centers Earned 282 million NIH from Clinical Research)*, *The Marker* (March 17th 2011) available at <http://www.themarker.com/news/1.605979>
- Melman, Yossi, *Medical panel: Anthrax experiments on IDF soldiers were unjustified*, *Haaretz.com* (2009) (Isr.), available at <http://www.haaretz.com/news/medical-panel-anthrax-experiments-on-idf-soldiers-were-unjustified-1.272877>

Ministry of Health Instigating Disciplinary Proceedings against 21 Physicians, available at News 2 website at <http://www.mako.co.il/news-israel/health/Article-50fc6a5b5702e21004.htm>

Nachmani, Nativ, Nisgar Tik Neged Harofeem Sheashu Nissueem Bebnai Adam (the case against the doctors who conducted experiments on humans is closed), Maariv (nrg) (2011), available at <http://www.nrg.co.il/online/1/ART2/210/794.html>

Resnik, Ran, The Ministry of Finance: The Senior and Specialist Physicians' average [monthly] income amounts to NIS 50-85 thousand (Misrad Haotzar: Hasachar hamemotzah shel rofeem bechirim ve momchim megeaaa le 50-85 elef shekel bechodesh bememotzah), (5.27.07) available at <http://www.themarker.com/career/1.445218>

Resnik, Ron, Mismachai Hanisuy? Ovedet Hanikayun Betach Zrka Lapach (Trial Documents? The Cleaning Lady Probably throws them to the garbage) Haaretz (No date), available at <http://www.haaretz.co.il/hasite/pages/ShArtPE.jhtml?itemNo=759382&contrassID=2&subContrassID=2&sbSubContrassID=0>

Rosenblum, Sharit, Anachnu Shphane Hanisyunut Shel Haolam (We are the Genius Pigs of the World), Yediot Acharonot (March 3rd 1997)

Vaysman, Paz, FDA to open ME office - probably in Israel, *Haaretz*, September 11, 2009, available at <http://www.haaretz.com/hasen/spages/1113611.html>

5. *Websites*

Israel

www.assafh.org (Assaf Harofeh Medical Center)

www.clalit-global.co.il (Clalit Health Services)

www.hadassah-med.com (Hadassah Medical Organization)

www.health.gov.il (Ministry of Health)

www.hospitals.clalit.co.il/Hospitals/Rabin/he-il/Pages/homepage.aspx (Rabin Medical Center)

www.hospitals.clalit.co.il/hospitals/soroka/he-il/Pages/homepage.aspx (Soroka Medical Center)

www.ima.org.il (Israeli Medical Association)

www.justice.gov.il (Ministry of Justice)

www.mevaker.gov.il (The State Comptroller & Ombudsman)

www.rambam.org.il (The Rambam Medical Center)

www.sheba.co.il (The Chaim Sheba Medical Center)

www.tasmc.org.il (The Tel Aviv Sourasky Medical Center)

U.S. & International Websites

www.aamc.org (U.S. Association of American Medical Colleges)

www.aau.edu (U.S. Association of American Universities)

www.clinicaltrials.gov (U.S. National Institute of Health database for Clinical Trials)

www.icmje.org (International Committee of Medical Journal Editors)

www.iom.edu (U.S. Institute of Medicine)

www.jama.ama-assn.org (The Journal of the American Medical Association)

www.oecd.org (The Organization for Economic Co-operation & Development)

APPENDIX 1: Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
AAMC	Association of American Medical Colleges
AAU	Association of American Universities
COI	Conflict of interest
CRO	Contract research organizations
DHHS	U.S. Department of Health and Human Service
FACA	U.S. Federal Advisory Committee Act
FDAAA	U.S. Food and Drug Administration Amendments Act 2007
GAO	U.S. General Accounting Office
GCP	Good Clinical Practice
Guidelines for Clinical Trials	Israel Ministry of Health Pharmaceutical Administration Guidelines for Clinical Trials in Human Subjects, 2006.
Helsinki committee	Hospital Ethics committee
ICH	International Conference of Harmonization
ICMJE	International Committee of Medical Journal Editors
IMA	Israeli Medical Association
IOM	Institute of Medicine
IP	Intellectual property
IRB	Institutional Review Board
MOH Special Committee	Israel Ministry of Health Committee for Contracts with Commercial Companies
MOH	Israel Ministry of Health
NDA	New Drug Application
NIH	U.S. National Institute of Health
OECD	Organization for Economic Co-Operation and Development
OIG	U.S. Office of Inspector General
PHS	U.S. Public Health Service
PI	Principal Investigator
Public Health Regulations	Israel Public Health Regulations (Clinical Studies in Human Subjects) 1980
REB	Research Ethics Review Board
SACHRP	U.S. Secretary's Advisory Committee on Human Research Protections
SGE	Special Government employees

**APPENDIX 2: Recommendations on Amending Israeli Regime Regarding Investigator
COI derived from the Comparative Analysis of U.S. & Israeli Provisions**

Category	FDA	NIH	AAMC-AAU	Israel	Recommendation
Purpose of financial disclosure	Ensure adequacy of clinical trial data	Advance objectivity in research funded by agency	Assure full awareness of potential conflicts & institutional efforts addressing them	Not indicated	Standardize objectives & responsibilities
Scope of disclosure	Significant payments paid by sponsor exceeding 25,000 USD; proprietary interest; significant equity interest in sponsor exceeding 50,000 USD or any equity in non-publicly traded entities	Remuneration exceeding 5,000 USD; equity interest of any kind; intellectual property rights & interests	Any outside financial interests directly or indirectly related to the professional responsibilities with de minimis threshold	Affiliation with trial sponsor, including employment, commercial or familial	Formulate extent of financial information disclosure, possibly with de minimis threshold to promote consistency
Updating disclosed information	Investigator must promptly update sponsor on financial interests status up to one year upon completion of trial	Investigator must update institution on significant financial interests annually or within 30 days of status change	Investigator should update financial interest information annually or promptly upon interim or material change	Not indicated	Require financial information updates at predetermined intervals
COI decision-making framework	FDA evaluates whether disclosed financial interests had impact on reliability of study while considering nature and size of interest	Institution evaluates whether significant financial interest could directly & significantly affect design, conduct or reporting	Institution evaluates whether financial interest may raise COI perception, with rebuttable presumption against participation by conflicted investigator	Not indicated	Create a clear framework for identifying & analyzing investigators' financial COI

Category	FDA	NIH	AAMC-AAU	Israel	Recommendation
Managing COI	Sponsors are required to take steps to minimize potential for bias	Institutions must develop & implement COI management plan; Should consider, inter alia, following strategies: financial COI disclosure to research participants; independent data monitoring; and modification to the research plan	Institutions must develop COI management plan. They should consider, inter alia, following strategies: independent data monitoring, disqualifying conflicted investigator, or divestiture of respective interests	Director of institution must ensure that no COI exists between investigator and trial sponsor	Develop selection of strategies to be implemented by institutions once prohibited COI is identified. Such strategies should maintain that disclosure in itself is not sufficient to protect against risks associated with COI
Investigator training on COI policies	Not indicated	Require investigators to complete COI training at least every four years or whenever investigator non-compliant	Provide adequate education on COI policies and procedures	Not indicated	Articulate mandatory COI policy and procedure training for all investigators conducting clinical research with human participants
Communicating disclosed information	Disclosure of investigator's financial interest information to sponsor, and sponsor to FDA	Post COI policies on publicly accessible website; publish all updated significant financial COI of key personnel	Communicate investigators COI in a human subject research to; inter alia, all researchers, students and trainees working on that research, editors of publication, and to the research subjects	Disclose information to institution, and in certain trials to MOH	Standardize extent of COI related information to be communicated and identify relevant audience

**APPENDIX 3: Recommendations on Amending Israeli Regime Regarding Government
Advisor COI derived from the Comparative Analysis of U.S. & Israeli Provisions**

Category	FDA	Israel	Recommendation
Definition to government advisor COI	Whenever particular matters of meeting have direct & predictable effect on advisors financial interests	Whenever conflicting interest is continuous & central to matter of opinion	Create clear definition to advisor COI. Define extent of relational associations between advisor and subject matter under review
COI decision-making framework	Prohibit advisors to participate in committee meeting if they or immediate family member have financial interest, unless a waiver is granted. Approving advisors eligibility includes multiple levels of review & assessment	Disqualify advisors with continuous and central conflicted interests to participate in meetings, unless a waiver is granted	Develop criteria to evaluate when conflicting interest is continuous & central to matter of opinion to merit participation recusal
Criteria for granting waiver	Evaluate whether advisors unique ability to contribute to committee outweighs their financial conflicts. Additionally, assess whether granting waiver is consistent with target rate caps	Evaluate whether advisors unique expertise outweighs their financial conflicts. Requires approval by the Deputy Attorney General	Develop criteria for granting waiver to advisors with conflicted financial interests. Develop selection of strategies to be implemented by MOH once a waiver is granted
Communicating disclosed information & waiver	Post on website financial interest information of advisors receiving waiver & reasons for granting waivers	Not indicated	Standardize extent of COI & waiver information to be communicated

**APPENDIX 4: Recommendations on Amending Israeli Regime Regarding Institutional
Research Reviewers COI derived from the Comparative Analysis of U.S. & Israeli
Provisions**

Category	FDA & NIH	AAMC-AAU	Israel	Recommendation
COI decision-making framework	Regulatory disclosure & recusal requirements for IRB members	Adopt clear & comprehensive COI policy for IRB members	Not indicated	Create clear framework for identifying, analyzing & managing COI for the Helsinki committee members. Formulate criteria for disclosure & recusal policy
Scope of financial interest disclosure	Not indicated in regulation	IRB member must disclose financial interest information with de minimis threshold	Not indicated	Formulate extent of financial information disclosure, possibly with de minimis threshold to promote consistency
Reporting non-recusal decisions to government agency	Not indicated in regulation	Not indicated	Not indicated	Create framework for reporting non-recusal decisions for conflicted Helsinki members to MOH for monitoring purposes
Communicating disclosed information	Not indicated	Not indicated	Not indicated	Standardize extent of COI related information to be communicated & identify relevant audience

APPENDIX 5: Recommendations on Amending Israeli Regime Regarding Institutional COI derived from the Comparative Analysis of U.S. & Israeli Provisions

Category	FDA, NIH & Israel	AAMC-AAU	Recommendation
COI decision-making framework	None exists	Institutions should develop and enforce institutional COI policy	Create a clear framework for identifying, analyzing and managing institutional COI
Definition to institutional COI	None exists	Whenever the institutional financial interests, or its officials acting on its behalf, might affect or reasonably appear to affect institutional processes for the conduct, review, or oversight of human subjects research	Create a clear definition to institutional COI
Institutional COI committee	Not indicated	Establish an autonomous committee in charge of conducting impartial review of institution financial interests. It determines whether these interests create concerns for COI. Comprise of at least one senior institutional official and one non-affiliated public member	Specify criteria to establish institutional COI committee and its objectives
Organizational structure	Not indicated	Separate human subject research from financial decision-making processes and agents	Create organizational barriers separating the responsibility for protecting human participants from institutional investment endeavors and technology transfer plans
Managing institutional COI	None exists	Impose rebuttable presumption against conducting research at institution with institutional COI. Compelling circumstances may rebut the presumption, following the COI committee approval and management plan	Develop selection of strategies to be implemented by the institution once institutional COI is identified. Such strategies should maintain that disclosure in itself is not sufficient to protect against the risks associated with COI
Communicating disclosed information	None exists	Institutional COI policies should be made available to the public	Standardize the extent of institutional COI related information to be communicated and identify the relevant audience

VITA

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