

Trust and Consequences: Biorepositories, Health Learning Systems,
and Beyond

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Abstract

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Abstract: The functions and nature of trust have been widely explored within the context of biobanks. As an established body of literature demonstrates, trust is believed vital for conducting modern research in which thousands of human tissue specimens are linked with de-identified information from medical records in a “Big Data” approach to finding genomic patterns and correlations behind disease manifestations. Without trust, the literature holds, potential donors are liable to refuse donation out of fear of weak data security or of researcher

misconduct. With transparency, security, oversight, and proper engagement practices, biobanks hope to secure donor trust. Trust is also important, albeit much less examined, in health care learning systems where a similar situation—researchers seeking to conduct research with subjects recruited within clinical spaces—prevails. Both biobanks and health learning systems are becoming increasingly popular means of finding answers to biomedical problems, and how trust functions in these settings cannot be overlooked.

Purpose: This dissertation aims to 1) examine stakeholder preferences, including those particular to trust and patient consent and engagement preferences, during the establishment of the Northwest BioTrust, a biorepository resource local to Seattle, WA, 2) qualitatively analyze IRB and patient views on trust as they apply to the health care learning model, and 3) explore significant policy ramifications remaining to be explored within the literature on trust in biomedical spaces. The overarching purpose of the project is to better inform research practices, to promote research obligations in trust-building ways, and to strengthen our research ecosystem.

Methods: My methods include: 1) semi-structured interviews with local biobanking experts and stakeholders, a focus group of King County citizens, and a systematic literature review spanning work published from 2000-2010 focusing on elements of trust and communication methods involving biobank donors and research participants, 2) qualitative content analysis of focus groups at leading Northwest clinics convened to discuss the ethics of research on medical practices, and 3) the linked advancement of a normative argument based on

relational ethics.

Results: Trust is critical, and in clinical spaces, potential participants prefer trust to be established relationally with one's care professionals, instead of with researchers or within research contexts; this characteristic adds important considerations to ongoing trust-building policy, particularly with regards to health learning systems.

Conclusion: Trust is relational and not simply transactional. Though consent forms are the most common way of seeking to build trust and of encapsulating donor and researcher expectations and duties, they fail to capture several elements of trust-building that merit consideration. Researchers should examine their assumptions about the regulatory and ethical duties they must discharge in the light of relational ethics.

“Deciding whether or not to trust a person is like deciding whether or not to climb a tree because you might get a wonderful view from the highest branch or you might simply get covered in sap and for this reason many people choose to spend their time alone and indoors where it is harder to get a splinter.”

— Daniel Handler, *The Penultimate Peril*

“In God we trust. All others [must] have data.”
-Bernard Fisher, MD

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INTRODUCTION

I am captivated by the concept of trust because its ubiquity in no way lessens its mysteriousness. We cannot pin down a precise definition of trust, yet we continue to measure the success of a wide variety of relationships based on the strength of the trust exhibited in those relationships. Trust acts like a bridge, rickety and wind-blown as it may be, between theories arrayed in the hallways of philosophy and the rough-and-tumble, dirty, near-unresearchable world with all its ambiguous complications and deeply meaningful impacts.

Trust, in other words, is useful. Trust has become increasingly useful within biomedical research, which is where I have chosen to examine it at play. Without authentic, functional trust, research and clinical operations risk devolving into empty transactions built on contractual obligation and fear or cynicism. With trust, these ecosystems of research and clinical treatment function more organically, can flex or grow as needed, and can result in networks of mutual understanding, dependence, and benefits based on relational care and the ethical obligations entailed therein rather than on the rote discharge of duties. Trust, theoreticians have posited, is the key scientists must master to open the door to public acclaim, approval, and continued funding. Trust intermeshes in complicated ways with the concepts of beneficence and autonomy; trust fits sometimes awkwardly into patient-provider, patient-researcher, and researcher-provider relationships. Be that as it may, how trust functions must be accurately understood within these elements, I argue, if research endeavors such as securing participants' tissue donations, obtaining participant consent for health learning systems research, or any of the other, increasingly complex activities taking place at the intersection of clinical and research aims are to succeed.

Within these aims, talk keeps swirling back, for me, to trust. Trust-building as an ethical duty. Trust as a way to leverage patient-provider relationships within the clinical space. Trust as a chimera of respect, information, choice, demonstrated

care, and reputation. The idea of trust, though it is supple and ephemeral enough to slip easily through biomedical researchers' carefully gloved hands, is nonetheless meaty enough to convince researchers that no ethical participation is complete without at least some modicum of it.

A number of the views I advance below on relational trust stand outside the understandings of trust being developed in clinical settings. I do not, however, wish to oppose how medical spaces and health learning systems try to foster trust—I instead wish to point to how various literatures and the work contained in this dissertation accentuate often overlooked elements of clinical practice and relationship-forging where more emphasis could be placed. I argue this emphasis should be honored where it already successfully exists in clinical care, and should continue as a deliberately designed part of biomedical ecosystems that add research practices to clinical care.

In this dissertation I first focus on trust and the daily business of consenting, storing, and distributing biospecimens related to the Northwest BioTrust, a complex research resource linking donors' biospecimens to studies. What expectations do donors have of researchers, and vice versa? How does a biorepository balance its many stakeholders' needs, and where does trust lubricate such an intricate apparatus? Do stakeholders even mean the same thing when they employ the term 'trust'?

After examining researcher, designer, and donor perspectives during the construction of the Northwest BioTrust, I segue into discussing the role of trust within research on medical practices and within health learning systems. Here I pose similar questions: what perceptions do patients hold of their care providers? How does trust factor into the patient-provider relationship, and how does trust enable or impede research conducted within clinical spaces as everyday care is dispensed?

Both biorepositories and health learning systems are—sometimes simultaneously—gaining traction as tools for welding research to clinical practice, or at least of leveraging research tasks within clinical spaces. As these practices become increasingly seamless, it is likewise important to track contractual obligations, as specified by a crowded regulatory landscape covering both clinical and research practices, and relational expectations.

As participant responses described in this second chapter reflect, documentation of consent is not always the piece of the consenting procedure most important to the patient or potential donor. Instead, it may be possible to waive documentation of consent under certain circumstances, and this may actually be a policy-driven step toward respecting donor wishes. The final chapter concerns itself with this normative ethical position.

Trust is the bright thread running through these various projects. Independently of each other, participants in both my Northwest BioTrust (NWBT) research and the work I did in affiliation with the NIH-funded “Ethics of Research on Medical Practices” project circled back to trust as a way to express the bond they feel with their medical team. Trust, in their words, both helps participants cement a caring relationship and express functional expectations—trust both repairs currently rocky consent conditions and paves the way for more respectful, practical interactions in the future as biorepositories and health learning systems increasingly fuse research with clinical care.

Trust conceptually bridges clinical and ethical duties—trust helps all entities involved understand how they are interwoven and what they expect from each other. Trust shows us where cracks in functioning relationships lie and also shows us how, for better or for worse, those supporting research with their tissues and their medical information prefer to be acknowledged. Whether they place their trust advisably or misguidedly in research integrity and whether or not they understand the tensions of everyday clinical practice and the rigors of

biomedical research, donors employ a language of trust to explain the consent choices they currently make and the ones they wish they were offered. Though researchers and clinicians may be more accustomed to an 'us versus them' dynamic, they, too, depend upon a language of trust and expectation between each other and in reference to patients which also merits examination.

I have settled upon trust because, ultimately, I do not yet see it being considered to its full potential—trust, I will argue in the forthcoming pages, can accommodate many more relational ethical considerations than it currently does, and trust as both a concept and a practice deserves to be more fully developed than the stage it currently occupies: a space for purportedly encouraging donor participation and staving off accusations of disreputable conduct by sharpening the edge of regulatory practice.

Policy cannot be sufficiently described by regulatory small-print, and humans, relationally disposed as we are, do not lean upon the concept of trust in very well- delineated or -proscribed ways. This is not to imply that trust need become meaningless or overly muddled if developed beyond regulatory purviews—I mean to say, rather, that the language of consent forms cannot fully choreograph trust. Trust is not a Big Mac or a thing easily dispensed to drive-through patients with a side of cheer. A discrete set of actions does not necessarily lead directly to a discrete amount of trust, and it is this idea I wish to further consider, to position trust more as a function of developing relationships than as the result of a set of regulatory steps.

In a nutshell, I will use these pages to advance my argument that relationally-developed trust is superior to regulatory-reliant trust because a) patients themselves tell us, in my work and in the literature from a wide variety of disciplines, including social science, psychology, bioethics, and research regulation, that robust relationships trump paperwork, b) relational trust offers care providers a transition from former patriarchal concern for patients to

smoother functioning within shared decision-making grounded in beneficence and respect, c) relational trust side-steps the shortcomings already established in current consent procedures (of truncated periods of time for decision-making, of decisional stress, and of the inadequacy of documented consent to reliably equate truly informed consent, among others), d) minority patients are less likely to feel alienated by consent conducted solely via consent forms and signatures. These are but few of the reasons I wish to argue on behalf of giving the development of relational trust primacy within spaces where research and clinical care meet.

My arguments should also be prefaced with a few caveats: we need not dispense with current consent procedures altogether, but we should also not rely upon them at the cost of truly informed consent, if we wish to uphold the values of respect for patient autonomy and of beneficence as we conduct research and administer care.

Second, relational trust does not apply solely to the relationships between patients and providers, though this particular kind of relationship has been the most widely studied in the literature I reference. Relational trust is important, I argue, in relationships between researchers and clinicians, and between patients and researchers as well—perhaps this work could function as a springboard to launch more investigation into how trust functions and can be developed within these relationships, though we start by examining patient-provider trust.

Third, I do not mean to argue that relational trust can *only* be developed in health learning systems by the direct care provider, though I do heavily interrogate trust within patient-provider relationships. These relationships are where the literature is thickest, though, by extracting insights from these relationships, I wish to determine, in future work, if they can apply as well to designated staff or even to technological applications, such as automated consent procedures—the point is that principles of trust should be preserved and refined in whatever context

research and clinical care meet, lest we lose the reality of truly informed consent and decision-making that respects how much each individual wishes to contribute to research within clinical care.

Perhaps relational trust does not “fit” elegantly into today’s quickly developing health learning systems, already constrained by the rigors of brief appointment times, heavy paperwork requirements, and the reality of patient-provider relationships that are not always long-lasting, consistent, or of high quality. But if we have room within health learning systems for research, I argue we also have room for developing trust, seeing what advantages it conveys and what damage occurs when trust is breached. We may wish to ask if giving trust a healthy environment in which to grow merits re-examining how we design our clinical spaces and clinical/research interactions with patients.

A last note: when trust is truly at play, it may be ‘invisible’—it may not be explicitly summoned up or invoked; it may simply be like the grease keeping clinical/research cogs running smoothly and safely. But when we are feeling hurt, betrayed, and exploited, in or outside of medical and research-related environments, we reach for the language of trust, which is likewise the language we use to describe our relationships with those we hold dearest. Trust, plainly, is not about safety. Trust is about risk, emotion, and many other “illogical” things that must still be taken into account, should any ethically responsible researcher/clinician wish to think about asking for specimens, for medical information, and, what’s more, for both the physical and metaphorical hearts and minds of those we hope will collaborate in tomorrow’s discoveries.

Chapter 1: Stakeholder Perspectives Solicited to Inform Development of the Northwest BioTrust: A Qualitative Study

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Introduction

The Northwest BioTrust (NWBT) is a bioresource meant to link specimens, both those already existing in pre-established biobanks and those being collected in ongoing procedures, with patients' de-identified electronic records information to facilitate easier specimen ordering during research studies. The NWBT's inception and subsequent construction has presented an excellent opportunity to solicit researcher needs and potential donor concerns and preferences with the aim of providing the NWBT with up-to-date, actionable recommendations to help guide development. This work was initially conceived of as a pilot project in exploring researcher and patient community needs and has been supported in part by the Institute for Translational Health Sciences, conducted with the approval of participating researchers Dr. Peggy Porter, Dr. Steven Schmechel, Dr. Nicholas Anderson, and Dr. Kelly Edwards. Site-specific, IRB-approved research was conducted primarily at FHCRC and SCCA.

Background

Human tissue repositories, known as biorepositories, are vital for strengthening research in cancer and other diseases with significant human health impacts (Fullerton, Anderson, Guzauskas, & Fryer-Edwards, 2010; Gottweis, Gaskell, & Starkbaum, 2011a; Winickoff & Winickoff, 2003). Large-scale collections of tissue and linked annotated data help answer important translational research questions with the potential to benefit both individual patients and overall populations (Fullerton et al. 2010; Gottweis, Gaskell, and Starkbaum 2011a; Winickoff and Winickoff 2003). Despite the importance of these residual specimens, however, no consistent policy or protocol guides how to ethically solicit specimens from donors or how to continue engaging these donors, if at all. An emerging body of literature has documented how research greatly benefits from properly executing informed consent and from engaging donors and the broader public during these collection processes (Gottweis, Gaskell, and

Starkbaum 2011a; Hewitt 2011; Trinidad et al. 2011), and it is important to continue dynamically developing this body of work as pertinent avenues of investigation and concern open up.

An opportunity to monitor prospective consent and engagement strategies presented itself during the foundation of a regional biorepository being designed in 2012. Several entities in the Seattle area, including the University of Washington (UW) with the Washington Phenotyped Biospecimen Resource (WPBR), the Fred Hutchinson Cancer Research Center (FHCRC), and the Seattle Cancer Care Alliance (SCCA) with the Cancer Biospecimen Resource (CBR) have been collaborating to create and administer a bioresource comprised of tissue samples and associated data intended to fulfill area researchers' needs for consistently-sourced, annotated tissue specimens.

The bioresource, eventually named the Northwest BioTrust (NWBT) after the completion of stakeholder engagement research conducted as described in this paper, allows researchers to request tissue specimens from patients with specific clinical characteristics and to collaborate in joint research more effectively—both these capacities accelerate biomedical research in the Pacific Northwest region and serve clearly identified researcher needs.

To facilitate ethically obtaining clinical patient specimens, the NWBT coalition expressed interest in fulfilling researchers' needs while also developing ethical patient engagement and consent strategies as the bioresource was being constructed. The field of biorepository communications has been growing, and certain consent communication and engagement strategies have by now been examined at length. However, not many of these studies or observations have been made in conjunction with a biorepository's start-to-finish design, construction, and completion. The NWBT's construction and its designers' related ethical concerns created an opportunity to ask participants pertinent consent and communications-related questions, the answers to which not only

support immediate NWBT needs but also advance the field of public-facing biorepository communications and consenting strategies in general.

Consent and Authorization for Use of Medical Records in Research: Collection and Storage of Medical Data on Solid Tumor Care and Cancer Patient (CODI) forms had been established at SCCA as a consent form requesting patient permission to include protected health information (PHI) in a cancer information database for use in IRB-approved research. Since CODI-eligible patients were considering questions very similar to those of the NWBT, I targeted these patients to discover their views on NWBT consent and communication procedures, which were judged likely to represent the views of patients ultimately being asked to give consent for tissue donation and anonymized medical records release to NWBT. While CODI does ask very similar questions in a format and procedure very similar to that proposed at the time for the NWBT, the NWBT differs from CODI in that it also requests permission to add residual tissue specimens to the proposed database, spans multiple agencies throughout the Pacific Northwest, and has the potential to involve commercial partners who may wish to purchase specimens for commercial drug-development and other biomedical purposes. The NWBT questions make similar technical requests for medical records data sharing, but are not restricted in scope to activities and sharing performed at SCCA or FHCRC, and thus widened the scope of impact along with, possibly, the risks participants are being asked to consider.

This paper describes preliminary investigations conducted to explore these questions via thematic analysis rooted in grounded theory.

Methods

This project sought to explore a range of stakeholder views pertaining to the establishment of a regional bioresource. Please refer to the Appendix for scripts used during interviews. To gather data:

- 1) I interviewed 11 biorepository-related specialists, including representatives from among consenting specialists, managers, laboratory scientists, bioethicists, nurses, community-based researchers, patients, and communication experts. Specialists had pre-existing ties with NWBT researchers and were recruited via email. Those interviewed included two specialists from racial minority groups, through the remaining were Caucasian. Specialists were interviewed with a semi-structured interview guide that solicited their a) biobanking-related knowledge, b) biobanking experience, c) perspectives on specimen sourcing, and d) views on consenting practices, donor engagement strategies, and related ethical considerations (included in Appendix 1). Interviews took between one half hour and an hour to complete and occurred at offices and coffee shops convenient for participants.
- 2) By email I invited researchers affiliated with UWMC and FHCRC who might be regarded as potential users of NWBT biospecimens to participate and interviewed eight of them using a semi-structured interview guide that asked about: a) the nature of their research, b) how they obtained specimens, and c) what strategies they recommended for consenting and engaging potential donors. One researcher belonged to a racial minority group; the rest were Caucasian. Interviews were conducted in subjects' offices and took an average of 45 minutes to complete. Subjects were between the ages of 30 and 70 and practiced clinically or as researchers primarily in Seattle, WA. Research subjects' scope of practice was comprised respectively of epigenetics, solid tumor research, blood and bone marrow transplants, colon cancer biomarker research, gene expression, genotype-specific targeted therapies, and pathological malignancies in bone and blood marrow.
- 3) Via email, I recruited community members who had been active in community-engagement conversations sponsored by the Northwest Association of Biomedical Research (NWABR). I convened a focus group and used a semi-structured conversation guide to solicit their views on: a)

the role of specimens in biomedical research b) potential names for the developing bioresource, c) consent and engagement practices the bioresource should consider, and d) specific patient engagement materials being developed for the bioresource. All participants were Caucasian; the focus group lasted ninety minutes and occurred in centrally-located coffee shop.

- 4) I recruited participants in-person at three SCCA sites and interviewed 10 eligible patients who were receiving CODI forms by using a semi-structured interview guide that asked: a) what the CODI form was seeking consent for, b) what their understanding of biobanking research was, c) if they would consider sharing residual tissue specimens and associated anonymized medical records with the NWBT, including why or why not, d) for their opinions of various names and consent/engagement strategies being considered for the NWBT, and e) their preferences regarding recontact and possible research updates. Eligible patients were those attending the Women's Clinic at SCCA, the Mobile Mammography Unit at Harborview, and the Heart Health Clinic at SCCA who were receiving CODI consent forms. Out of 16 patients approached, 14 agreed to the in-clinic interview, which lasted 10-15 minutes. Four were called to their appointment during our interview or were otherwise unable to complete it, leaving a total of 10 who successfully completed the interview guide and related questions. Interviewed patients signed a research consent form for this study, were given background information on NWBT's goals, and were left with a flyer describing study aims. If specialists or researchers consented, I recorded their interviews and transcribed them. All other interviews, including patient interviews where patient recording was not permitted, were documented with extensive notes. Transcriptions and notes were analyzed for emergent *de novo* themes across the range of interview guide topics discussed and were then coded.

Results

Specialist Interviews

Specialists were recruited across a wide range of community-based roles in King County and not all specialists chose to focus on the topics presented in identical depth. Specialists were all familiar with the types of research conducted using human tissue specimens, and most specialists had experience in consenting patients, in conducting research with specimens, or in considering the ethical implications of biobanking research. For additional information, please refer to Table #1. Interview data broke down into the following general categories:

Perspectives on specimen sourcing

Specialists were familiar with current ongoing research using specimens. They approved of biobanking-related research in general and advocated for sharing specimens and related annotated medical records as research resources. Specialists felt research using human tissues specimens could lead to important discoveries, particularly for minorities and specific disease populations—this applicability fueled participants' sense that research should be well-supported and that specimens' potential should not be wasted. Though participants were sensitive to how minority populations had been exploited in the past, they wanted to encourage minority participation, lest important disease markers specific to particular populations be overlooked.

I don't feel we have time to waste. I hate to see samples wasted.

Laboratory technician

Choosing not to donate means you're being left out of research advances.

Laboratory technician

Views on consent practices

Specialists had considered consent protocols at length. While they approved of it and believed obtaining consent to be essential for securing specimens for research, they identified a number of concerns with current consent protocols.

The following sub-themes emerged:

Consenting is necessary but not currently effective or sufficient

General consensus confirmed that consent was believed to be important, albeit relatively ineffective as currently conducted. Little incentive currently exists for specialists and clinicians to take extra measures in explaining and obtaining consent for specimens intended for research purposes instead of clinical purposes—this kind of mission caters to the needs of researchers considered somewhat peripheral to clinical tasks and is perceived as an additional burden on already strained admissions specialists and nurses. If the consent process is not built seamlessly into clinical routines, subjects perceived little chance of consent truly succeeding. If consent was an optional effort, participants testified that it would be quickly disregarded.

There are so many tasks that you have to do when you see someone, and you skip over so many important tasks as it is, that that's [explaining the implications of consent] a zero priority task.

Consent specialist

Significant barriers currently block successful informed consent

Clinical communication currently can obstruct successful informed consent. Nurses, specialists said, frequently hesitate to enforce consent when they do not personally witness the consent or are unsure of a new consent procedure. Furthermore, a multiplicity of studies being conducted simultaneously in a clinic, attendant with their multiple consent forms, can confuse patients. Currently it is not unusual for a clinic to be using up to five different consent forms, depending on the type of associated research being done—the consistency of wording in these consent forms is often low, and consent protocols are uneven. Messages were being lost in the process, specialists felt—for example, rare specimen donations were particularly valued, due to restrictive eligibility criteria and the difficulty of sourcing these specimens. Other barriers include the fact that patients often want admissions specialists to connect emotionally with them, and prefer this connection over the formality of signing forms. Language barriers

present a final stumbling block—translation services are available at some sites, but often cannot meet demand in a timely fashion.

Communication is very disjointed right now.

Clinical coordinator

I feel sad when I'm not able to explain the form to them.

Admissions and consenting specialist

To do this job takes very strong people skills. You get thrown into the den with the lions.

Admissions and consenting specialist

Some clinics had considered hiring dedicated staff to hold consent conversations with patients within the waiting room itself but had been discouraged from doing so by issues of cost and the availability of unused exam rooms or other private locations for consent conversations. Private exam rooms had been used in some circumstances, but their availability was reported as unpredictable.

Timing was also an issue. Some patients were being given consent forms directly before surgery, when consent specialists felt conditions might subject patients to difficult or complex decisions in an already taxing time period when patients were already likely to feel vulnerable and stressed. It would be more ideal, specialists conceded, to speak to patients personally, but this was not considered possible, due to how far behind appointment times clinics were already typically running. Consent procedures, it was felt, would add yet another cumbersome, time-consuming step, especially when done personally instead of asking patients to sign a consent form. Telephone consenting had been contemplated, and one clinic already had developed an IRB-approved script for telephone use after setting a surgical date with patients but before surgery occurred. Overall, however, consent conditions were considered far from ideal.

Sometimes it's awkward to use a script, and you just want to talk to a patient. Really, we just want them to know what will happen.

Consent specialist

We can only consent right before surgery right now, and it's not ideal.
Consent specialist

Views on participant engagement

Although discussing emotions is not perceived as very clinical, participants thought researchers should work to step farther away from relatively sterile-feeling consent conversations (or forms administered without any conversation at all) and should concentrate instead on seeing donors as humans with powerful emotions and stories that should be acknowledged and engaged.

Make it real—tell real stories. Handing forms over isn't sufficient.
Communications expert

Get away from the research-based paradigm...Make it easy for stories to emerge organically.
Community based participatory researcher

Patient motivations to donate, as relayed by specialists, included a strong desire to spare other patients the stress and pain they had experienced. One specialist emphasized: “Empathy incentivizes people.” Anecdotally, breast cancer patients and their families are particularly motivated to participate, especially when approached by female consent specialists.

Focus on the good.
Community Nurse

Researchers have community responsibilities as well

At the same time, participants did not automatically trust the “business” of science and government spending on research they deemed potentially inefficient. They acknowledged how science preserves its own disciplinary eccentricities and protocols but did not think these disciplinary mores exonerated researchers from exercising reciprocal responsibility to participants in exchange for tissues donations and trust. Instead, they encouraged researchers to carefully

consider benefit sharing and how responsible benefit sharing could result in helpful ongoing relationships, while unequal sharing could succeed only in the short term at best and at worst could be exploitive. All “players in the game” need to be credited for their contributions and need to share information and respect. Without this respect, participants worried that scientists might overstep moral boundaries or might exploit and colonize vulnerable populations instead of recognizing their invaluable contribution of cells. Researchers need to be very careful with how they allocate their resources and how they conduct their work, interview subjects reported.

Some scientists seem lazy and elitist, willing to pad their budget. The government encourages extra spending by how experiments are funded.
Laboratory technician

Human bodies have become new frontiers of exploration and colonization...People are upset when money and careers are founded on others' tissues.
Bioethicist

I can't imagine saying 'no' to donating tissue for research. That's because I have a certain trust in how research is conducted ethically. Without that knowledge it'd be spookier.
Cancer patient

A culture of sharing is important

Sharing, in the sense of donating specimens and of sharing knowledge, was supported, and participants thought leaders should work to cement a “culture of sharing.” This includes researchers sharing their work with the community and actively seeking to prove their trustworthiness, particularly with minority populations.

Specimen donation itself is low-visibility and patient awareness of what it entails is often even lower. If the concept could be higher in visibility, could be more “branded,” or could at least be more consistent across different Northwest clinics, teams could at least use roughly analogous consent language, specialists said,

and would likely feel more cohesive and more comfortable knowing they were using similar terms.

In the end, however, specialists saw little chance for overall improvement until large-scale media and culture-shifting campaigns portray specimen donation as a rare, exciting contribution to valuable research and succeed at both publicizing biorepository-based research procedures and attendant repercussions.

Researcher Interviews

I interviewed eight clinical and research professionals who had used CODI specimens in the past or were interested in more widely incorporating NWBT specimens into their ongoing research endeavors. Researchers are not identified by specialty due to anonymity concerns. For additional information, please refer to Tables #2 and 3. Emergent themes included:

Specimen sourcing can be very challenging

Researchers reported obtaining specimens for their research from a disparate and widely varied number of sources. Affordable, research-ready sources from industry channels are rare, subjects stated, and industries are more likely to want to take advantage of university-associated biorepositories. Relying on universities to found and administer biorepositories can be unsatisfactory because it can wall researchers off from biorepositories at other universities, thereby constraining researchers' studies to the availability and collection methods of locally available biobanks.

It's difficult, because the people who are developing the biobanks are doing it for their own institutions.

Subjects expressed a great deal of frustration about current specimen sourcing conditions, particularly when trying to locate and order specimens within the

University of Washington Medical Center (UWMC). They reported the existence of six separate specimen-ordering systems of near-Byzantine complexity instead of a single centralized system, and testified to the prohibitive effort and complexity involved in navigating these various systems:

Physicians [at a major Northwestern health care system] have a huge problem: [There are] Six information systems, whereas real modern hospitals have one. Let's say tomorrow you snapped your fingers and had a discarded blood system, it would still not be possible to do the same queries as other hospitals... Residents have cheat sheet, to access the different systems, and nobody's integrating. People here just don't know better.

IRB requirements were often perceived as cumbersome and difficult to navigate. Changing IRB requirements and institutional attitudes that were perceived as obstructionist or uninformed presented researchers with serious challenges.

One of the frustrations, every time we want to get samples, there are ad hoc collaborations and IRB approval. Right now we're getting muscle biopsy samples, and it prevents us from doing some of the things we'd like to do with fresh muscle biopsy samples. We're trying to set up a collection ... but going through the approval process is incredibly difficult...and so, in the absence of getting the tissues, it's a delay in progress to developing therapies. I'm so used to it at this point, I've never known a system that works any better--- if you guys can get a system that works any better, that would be amazing.

As residency fellows, we had to sit in on IRBs. Because of so many kinds of research being done, the IRBs operated very efficiently and were really effective. The IRB here is not staffed by people doing research. I don't understand why the IRBs here need to be so cumbersome.

Harvard's discarded blood system is amazing, and it's stunning how it affects their ability to conduct studies. Here we get tissues from the Hutch and from a rotating pool of regular donors. There is a lot of bureaucracy here—my wife, for example, had to get tissues from Boston instead of here, because of how long it would have taken to procure samples and get approval. This place has a "can't do" attitude.

Just thinking about getting a new source of tissue is a real headache for me, because I have to relearn all the protocols for getting human subjects and IRB approvals.

Other barriers to procuring specimens included funding restrictions due to the high costs of maintaining biobanks, the lengthy amount of time to set up the collaborations needed to access certain specimens, complicated paperwork, bottlenecks when particular researchers or institutions control certain disease banks strictly, and the difficulty of writing successful tissue-procurement applications. Less frequently-mentioned issues included coordination challenges when trying to obtain fresh specimens and problems with guaranteeing biorepository maintenance. In response to these challenges, subjects sometimes chose to work with readily available tissue specimens outside of their direct research interests rather than pursue research dependent on specimens that were less readily available.

I don't mean to be a whiner, but it's a lot of work.

It's very difficult to fund biorepositories, very few venues pay money to do this... Mainly for the specimens we collect locally, it's mainly a staffing issue. Staff are positioned so that they're available when the patients are available. Because of coordination with the operating room, getting the samples when they're fresh is a challenge.

Right now it's ad-hoc, one-off.

Consent considerations

Donors appear quite eager overall to contribute specimens

In researcher views, most patient population donors, when approached in clinical settings, have been very receptive to being asked to donate specimens. Specific disease communities give potential donors an identity to rally around and a tangible action to take in combating the disease.

Patients have been very willing to participate by donating tissues, and often we'll have emails or calls asking how can I give something like this – the barrier is not [having] an easy entry route for people to do that.

There's a sea change in how people see their disease now, and [they have] enthusiasm to contribute. They're highly motivated. Pediatric cancer communities, for example, were working in Huntington's. These patient communities are some of the most motivated people you could imagine working with. I've not run into patients not wanting to participate as any barrier at all.

Through these activities I have had a lot of interest from patients' families. Because of this organization I have developed a better way to say what I do and why this would be important.

Of those researchers who had experience with direct recruitment, they recognized that not all patients make enthusiastic donors, however, and thus tended to reassure concerned patients who were potentially unwilling to donate that they need not feel compelled to do so, and that reluctance or refusal was perfectly acceptable. Researchers did harbor concerns that in some cases patients might suspect a “link” between their donation behavior and the quality of their care, or might believe donation might somehow directly benefit them.

I've had people who were deeply suspicious of the research enterprise, so when I come up against that brick wall I say, 'OK, you don't have to.'

Some are truly altruistic and I suspect what's going on emotionally is they're saying to themselves 'If I'm a good person, God will reward me.'

Researchers say consenting procedures that feel personal are important

Dedicated staff were judged necessary for successful consenting. Though researchers could agree on clinical spaces being the proper location in which to conduct consents, they wondered if the consent process could be better supported by mailings or other invitations to participate that could allow patients more time for contemplation outside the possible perceived pressure of clinical

environments. They also wanted consenting to contain a personal element so the process did not feel so cold and passive.

Articulate it clearly. Everybody's really sick and tired of "Can I take 5 minutes of your time?" We need dedicated staff. Nobody says anything about it right now... It's not like someone says 'by the way, there's research consents here,' it's just so passive. Being aggressive isn't necessarily the right thing either, but I don't know why...I know it's got to be clinics, but I don't know why the head of each clinic couldn't mail those people a letter.

I've heard of labs appealing directly to a patient population, and if it's a pretty rare tumor, they'll talk to patients directly, and their families will be interested in donating directly. Having a more personal connection could help in encouraging tissue donations.

Engagement strategies

Researchers also valued specific donor engagement and education practices

Researchers thought participating in research could feel beneficial for donors and wanted solicitations for donations to accurately convey powerful opportunities to help other individuals.

In the New York Times last Sunday, a professor at Wharton, he said what motivates people in companies is the idea that they're helping somebody. He's done a bunch of studies that prove this. It left a deep impression on me as I read it this past weekend...it just has to be true in almost every human arena. That's the most powerful emotion you can give anyone.

People fell like they did something. People understand that this is how progress is made.

Get them jazzed up about wanting to give. Get people to respond when they know they can contribute to something really good. Somehow reaching them in a more personal way.

Researchers did not think donors needed to know all the specifics of the research being done with their specimens.

The main thing is that we'll be collecting the tissue so it doesn't create any extra risk procedurally, but there is the possibility that their EMR and HIPAA will be accessed, because of confidentiality. But also they're aware of potential benefits and of biospecimens advancing effective medical care. Personally I don't think they need to know the molecular things we'll be doing.

Researchers are willing to participate in donor engagement

Researchers advised NWBT designers to use personal stories, quotes, and narratives about the deep satisfaction to be derived from contributing specimens when communicating with potential donors. Though they expressed some hesitation over their own levels of communications and outreach expertise, participants were generally willing to attend donor meetings, testify to the worth of annotated specimens in their own research, and otherwise contribute to supporting community-facing biorepository messaging. Subjects showed wide support for newsletters, a biorepository website, and ongoing communication channels to inform donors about research progress.

It's hard to tie a residual specimen to saving someone....that's a long road. I guess finding someone who did derive deep personal satisfaction from doing this, get a quote from them.

It's important to universally deliver the message of why these biospecimens are important to accrue, to advance medical care and knowledge.

Commercial ties should be acknowledged

Researchers were cognizant of past communication failings and were sensitive to donor perceptions that researchers might be making their fortunes and careers based on uncompensated tissue donations. They felt that commercial ties should be acknowledged and that donors should understand the role commercial entities play in accelerating the therapeutic drug pipeline. They did not recommend underplaying the money companies make in these endeavors, but also wanted to

emphasize the message that whole patient communities could suffer from slow drug development or lack of attention if they are not willing to donate specimens.

It's important to address upfront what about financial interests. The story of [Henrietta] Lacks is on everyone's mind, and unfortunately that story has put out the notion that scientists make billions of dollars off their biological samples.

Somehow conveying the sense that the samples will be for research purposes, what will be the commercial value. If you prevent commercial usage, it prevents drug development. There should be some succinct way of conveying that.

Researchers mention the importance of trust

Donors' trust in research was worth considering, from researchers' perspectives—researchers mentioned the Havasupai case in several instances and pointed to how this damaged trust. Participants felt trust could be better built by demonstrating the training in data security researchers and clinicians are given and how they are held accountable for maintaining data confidentiality. Placing clinical trials online and showing how specimens were involved was also thought important.

[Trust] keeps being undermined by bad stories in the lay press, like the Havasupai story. That's really ugly when that kind of stuff gets into the press. Good news doesn't make the paper.

[Trust can be built by] Just maybe explaining all the protocols and how they're standardized and how the researchers and clinicians go through HIPPA training and confidentiality clauses and what the methods are that are used for research and how that's accountable. Also I think probably the fact that you can look up clinical trials online, that they have access to that information.

Researchers have well-formed ideas of what they need to accomplish their work

Researchers reported that having an automatic structure in place, both for requesting specimens and for identifying appropriate patients who might donate

specific types of specimens, would be helpful. Many of the researchers interviewed were willing to collaborate with clinicians and other laboratories to facilitate an easier exchange of more varied tissues. Current difficulties with obtaining suitable specimens have been hampering ongoing work, researchers reported.

We can't easily get through the IRB approval process, and, due to tissue procurement issues, we're being held back from developing proper animal models for muscle diseases, and we're also being delayed in developing new therapies to address specific disease mechanisms. It would be wonderful to have a centralized clinical research committee to work with IRB protocols.

With decrease in funding from NIH and other government sources, it is really important to figure out at SCCA, a push toward finding other ways to get funds for research and to continue the work we're doing. Emphasizing that would be helpful, and that once a diagnosis is made, although we store all the tissue, if we could get access to it after the clinician is done, it could be helpful for the patient.

I would like to see a catalogue to see everything that's available and how well it's annotated so I can get what I truly want. I would want to know layers of that – what kinds of specimens have been collected, how they've been stored, and how difficult it might be to get at them, and what info is attached. ...If all those ducks line up: I see what I want, I can order it, I can afford it, I'm a user.

Having a central group that I could tap into as a resource that would be up to date every time I needed to get a source of tissues samples would be helpful.

To some extent, gets into a tricky issue, we're not willing to just give them away – we've put our own blood, sweat, and tears into them.

Focus Group Responses

Focus group members agreed that biospecimens-based research is important, but displayed a wide range of knowledge about the specifics of this sort of research. Members held a variety of feelings toward research ranging from support to fear. Focus group members participated in a discussion directed by a

topic guide and their responses to specific topics were recorded. For additional information, please refer to Table #4.

NWBT preferences

Focus group members preferred 'sample' instead of 'specimen,' and were split 50/50 over 'Northwest BioTrust' and 'Seattle Health And Research Exchange (SHARE)' as a name for the WPBR/CBR (Slattery/Porter) biorepository.

Consenting

They preferred, to a member, to be asked for consent in person, and were also generally willing to donate their specimens.

Patient Interviews

The 10 patients interviewed at SCCA sites concurred on a number of themes: a) what the CODI form was seeking consent for, b) what their understanding of biobanking research was, c) if they would consider sharing residual tissue specimens and associated anonymized medical records with the NWBT, including why or why not, d) for their opinions of various names and consent/engagement strategies being considered for the NWBT, and e) their preferences regarding recontact and possible research updates

Patient understanding of the CODI consent form

Of the 10 patients who completed the semi-structured interview, only five could recollect what the CODI consent form they had signed within the 10 minutes preceding the interview had asked.

Patient understanding of biobanking practices

Patients confirmed NWBT developers' suspicions that patients are sometimes confused or conflicted about how human specimens inform research.

Patients do not always know much, or want to know much, about how specimens contribute to research

I don't know anything about them [speaking of specimens].

I don't know how much money or samples goes [sic] to research, but I'd be interested to see how it happens. Everything is developing so fast. I don't use a computer or want any more literature though—I'm not as interested in the research itself. I want to get it over and get it behind me.

Patients, in general, support biobanking-based research

Despite their general lack of understanding about biorepositories' function or about how specimens contribute to research, 80% of participants still thought research was important and were still willing to consent to donate their residual tissues and share their medical records. Empathy and altruistic feelings played into this willingness to share and contribute. Other motivations for donation included preventing the waste of collected tissues (40%) and to “feel good” about themselves (20%).

The idea of furthering research to possibly create some relief to someone else in a similar situation—that possibility, to help the future, is very attractive.

Research is the best way to keep thinking and growing.

Patient willingness to donate specimens and to share medical records

Patients do not appreciate commercial ties

Participants did view specimen collection and collaboration with private industry as suspicious.

They're creating an empire of value based on my samples.

There's nothing altruistic about it.

Patients prefer consenting protocols that feel personal

Supporting documents, such as handouts, are valued, and respondents said they would be likely to refer to a NWBT website for information and updates, but they still preferred actual consenting to occur in person. Respondents said, given the limitations of the clinical space, that they could accept signing consent forms as part of the front-desk check-in procedure, but that they still preferred to do consenting in person with a chance to ask questions and get clarification on what they are being asked. This consultation should occur at least a few days before surgery (as opposed to some of the surgery consents currently being solicited in the hours directly preceding surgeries in the NW region—respondents identified the pre-operative consultation as an ideal locus for NWBT consenting and thought day-of consenting was “insensitive”). Whatever solicitation channel is used, subjects preferred personalization and the feeling of being invited to participate.

The idea of creating an invitation is key.

Limitations

The work reported herein was conceived of as a small initial study and may not be widely generalizable. The small number of subjects interviewed implies that saturation in all areas of the interview guides was not achieved. Since some interview subjects were selected due to their involvement with NWBT researchers, bias may also have been introduced. Additional limitations are presented by the fact all coding was completed by the author. CODI consenting procedures had already been conducted with most eligible patients prior to the study, and so not many eligible (pre-consent approach) patients remained to recruit.

Discussion

Given that biorepositories are not always high-profile discussion topics in public spheres, it appears possible to secure wide public support of biorepository-driven

research as long as repository donors trust the research entities involved (Gottweis, Gaskell, and Starkbaum 2011a; Goddard et al. 2009; A. A. Lemke et al. 2010; Trinidad et al. 2011) feel they receive something in return, such as respect and research updates (Meulenkamp et al. 2010; Vermeulen 2011; McCarty et al. 2011; Hewitt 2011) and feel that their personal information remains secure (Kaufman et al. 2009). My findings confirmed these statements while highlighting potential donor support for education and increased interaction (particularly in-person) around consenting actions. Potential donors desire ongoing communication, regular updates, and ways to learn more about biorepositories if they so elect.

Current regulatory practices have emphasized privacy and data security (Anderson & Edwards, 2010) without attending to the dimensions of reciprocity and trust inherent in these public interests (Trinidad et al. 2011), and my findings continue to point to the importance of relationally-based, person-to-person interactions over protective regulatory guidelines for consenting and engagement behavior. Personal interactions seemed more pressing to subjects than did concerns about data security.

Patient subjects echoed specialist subjects' assessments: though they still remain relatively naïve regarding how specimens are currently being used in research, they nevertheless support such research, particularly when research goals are clear and researchers are willing to report updates and recognize patient contributions. The literature documents the powerful role of empathy and altruism in biobank-related donation behavior, which my study's subjects echo. As one participant put it: "Empathy incentivizes people." Patient participants testified to their willingness to help other patients, particularly if it would spare others the negative experiences they themselves had already endured.

Though most patients and other participants interviewed were willing to donate specimens, SCCA Human Protection and Research Implementation Coordinator

Steve Johnson has reported that between 5-10% of patients at SCCA decline the CODI consent questions, usually citing concerns about confidentiality or about the perceived likelihood of researchers capitalizing on freely donated patient specimens for their own welfare.

Family members, specialists said, often supported specimen donation and could pressure patients to consent, even when the patient was indifferent or ambivalent. Specialists, therefore, were concerned that patients might not perceive specimen donation as being truly optional. In their estimation, about 5% of patients at a particular clinic harbor concerns about HIPAA and related confidentiality issues regarding their potential donation, and preferred not to make this decision so close to their surgeries.

Though it would not be sufficient to simply improve consent forms, which 50% of patients interviewed are not currently able to accurately remember, designing simpler consent forms and shifting part of the consent procedure into the examination room itself, where patients could experience consent as a bidirectional dialogue instead of “sterile,” often confusing or unmemorable consent form would be a positive step toward consent and engagement procedures that fit patient preferences and increase the likelihood that patients’ concerns will be allayed, their tendency to consent encouraged, and their desire to feel respected while being offered an autonomous choice honored. Both direct patient testimony and patient preferences documented in the literature highlight the inadequacy of consent forms for patient education, behavior change, engagement or, arguably, informed consent itself (Luque et al. 2012).

The NWBT project occupies an interesting ethical and legal position—while the NWBT is not obligated under current law to inform patients of how it disposes or banks residual tissue specimens, the NWBT, it can be argued, has a responsibility to acknowledge these preferences, or at least could arguably benefit clinically in terms of obtaining higher patient consent rates and, hopefully,

a more trustworthy reputation by changing its practices based on patient feedback.

For example, UWMC patients have explained how consenting directly before surgery is uncomfortable and feels rushed—UWMC managers concur with this assessment, but are currently struggling to redesign clinical protocols to enable better consenting without overly disrupting clinical proceedings. This discomfort, though procedurally inconvenient, represents an opportunity to examine current consent strategies and re-evaluate them to see if they could be reconstructed to better fit donor preferences expressed both in the literature and by this study’s participants.

Tension exists regarding who, exactly, should conduct consent. Current practices position consent at the admissions desk or prior to surgery, primarily via a signed consent form, but evidence indicates that both clinical staff and potential donors themselves would prefer alternate consenting methods. Physicians’ assistants and nurses, specialists reflected, felt they had little stake in biorepository consenting, and surgeons were perceived as natural choices for explaining consent, since they exerted “a type of influence they’ll [patients] take more seriously.” While surgeons had been open to this role, in specialists’ experiences, they experienced difficulty in following through, due to forgetting this particular task among the other threads of patient-provider conversations and to the conflict this consent requirement, one more task on an already long list of conversation topics, introduced for clinical managers charged with keeping clinical appointments running smoothly. Understandably, doctors are not anxious to add another duty to the long list of tasks they must accomplish during a patient visit. This tension could be a rich source of continuing analysis.

Specialists and researchers interviewed displayed sensitivity to donor concerns and agreed in many key areas about the importance of in-person interactions

about donor education. Most participants agreed that specimen-based research is important and should be supported.

All participants also wrestled with areas of frustration—for researchers, obtaining specimens in the Northwest region is clearly a struggle. This need, I argue, could be amply met by willing Northwest donors if certain requirements could be met.

As supported by the literature, potential donors prefer to donate after knowing what kind of work their specimens will support (Gottweis, Gaskell, and Starkbaum 2011b). One successful method for conveying research successes involves narrative strategies: bringing research narratives to life by encapsulating them in stories about real patients. Narratives, particularly stories set in appropriate cultural and/or spiritual contexts that are coupled with substantially useful information, are recommended (Campbell et al. 2004; Gibson 2007; Viswanath and Emmons 2006), and their appeal is confirmed by this study's participants.

Independently when interviewed, patients, clinicians, and communications specialists highlighted the educational work narrative storytelling can perform by building empathy and embedding facts within a comprehensible, memorable story. Lacking these stories, clinical spaces forego an opportunity to convey messages effectively and risk implying that research breakthroughs may not travel far enough to reach them personally. As Marks and Reed remind us, patients do not want to see breakthroughs that will not trickle down to them—they want solid information, graphics, and applicable stories; they want to see “messed-up cells” and doctors working to find solutions (Marks and Reed 2004).

Interviewees identified a few other important factors. Financial interests will be on donors' minds and should be acknowledged upfront. Additional education may be needed to illustrate why collaborations with pharmaceutical development companies may be desirable and may not necessarily conflict with donors' goals.

Since donors may perceive these kinds of academic-industry collaborations as a risk, biorepository designers should be upfront about the possibility of these involvements, as well as their plans for brokering these relationships and collaborations (Churches 2003; A. A. Lemke et al. 2010).

Patients in my study pin-pointed their preferences: to help them learn what their specimens accomplish, the contributions they make need to be highlighted in terms of personal differences being made. Stories featuring other patients could assist with this, and patients were upfront with their desire to hear about these differences through researcher talks, in-person clinical consultations, or emails. Newsletters or website content was also valued, but patients in general did not appreciate being asked to contribute tissues as an admissions-based, impersonal consent process. When asked what information they would find trustworthy when seeking to discover more about biorepositories and research, respondents said they would like to get their information from reliable websites and by word-of-mouth.

Respondents want to see how their donations are being valued and used—a personal invitation to donate, coupled with personalized updates (if possible) or at least with general updates that ‘prove’ their specimens are being put to good use helping others were thought very appealing.

While they did value different ways to receive information, they recognized the need to keep this information fairly straightforward and simple as well, which again finds an echo in recent literature (Beskow et al. 2010). Patients appreciated having ways to find out more about tissue-related projects without hearing all the details upfront, but they did want to hear the general outlines and to receive credit for their own bodily contributions, or at least a ‘thank you’ as an acknowledgment of them having considered a significant decision and determined to donate in the face of some risks. The ‘thank you,’ were it to be a card or regular expression of gratitude reminding donors of researchers’ ongoing

appreciation, could also function as a way to communicate updates. This possibility found favor with surveyed admissions specialists and UWMC managers, and falls into line with recommendations made by interviewed patients and bioethicists. The money being made by researchers and for-profit organizations could sometimes give patients pause, but they did not always expect or desire a share of this money so much as they craved acknowledgment for their choice and an ongoing source of information about what beneficial impacts they—at a remove—continue to make. Clarity was very important to respondents, as well as putting effort into making biobanking and related research understandable and inviting.

Communication should not cease after this initial consent interaction, however. As one of my interview subjects, a community nurse, testified: “healthcare education is a cumulative process.” Patients appreciated ongoing communication and updates, particularly ones catering to their expressed preferences of using websites and email as chosen communication channels for educational updates. Brochures and hand-outs, staples of in-clinic educational campaigns, were not viewed favorably by either patients or by admission specialists, and were believed to be largely dispensable.

Limitations

This research’s reach is constrained by several limitations. Saturation was not likely reached in all question categories. The specialist and the researcher interview subjects, as well as the focus group members, were recruited through convenience sampling and snowball recruiting, which could result in systematic bias. Finally, views expressed by subjects in this study are not necessarily widely generalizable, due to the small sample sizes and to their demographic niche as Northwest cancer patients. Even given these limitations, however, this study’s findings do align with views established in the literature and indicate a helpful and actionable range of area perspectives to both help guide the NWBT’s ongoing development and to inform future biorepositories.

Many opportunities to further pursue questions raised by this study exist. Future research could concentrate on expanding interview sample sizes, on advancing minority perspectives within these spaces, on fine-tuning preferences around engagement strategies, and on delineating areas of tension between the needs and desires of researchers, clinicians, and potential donors.

Recommendations

Based on my work so far, I recommended that the NWBT:

- 1) Develop a clear, easily-explored website that conveys transparency, educates patients, and explains the community involvement that occurred during its formation. The website should include clearly listed contact information, clear narratives, and text of consent forms and other supporting informational/educational documents in easily accessible ways. The NWBT has developed a website with my assistance: <https://www.nwbiotrust.org/en.html>, but developers can continue to refine and improve this site by remaining attentive to patient preferences.
- 2) Using multiple media channels for patient information (including judicial email, opt-in newsletters, and mailed hard-copy thank-you cards). This gives patients more choice about the level of information they prefer to encounter and navigate and gives donors a means to track the ongoing work their specimens may be involved in.
- 3) Express researcher gratitude clearly (via cards, in-person presentations, emphasis at time-of-consent). This should be a consistent, prominent message, and will be better received if researchers or clinicians can convey it during in-person consultations.
- 4) Show how specimens help research, and, ideally, individual patients via strong story-telling in-person and online. Stories can do much more heavy lifting, when it comes to useful health marketing/behavior change/appealing responsibly to emotions, than statistics and “dry”

- information typically can. These stories should be personal, warm, and vibrant (not “canned”). Video, sound-recording, and other kinds of documentation are all viable ways to convey research messages.
- 5) Provide other opportunities for patients to learn about biobanking and consider the consent questions they’ll be asked other than solely the moment of consent expected at check-in (suggestions include billboards, emails, broad campaigns). This relieves some of the burden on the moment of consent, makes biobanking and health learning systems endeavors seem more of a campaign, and becomes an on-going opportunity to tell stories and connect with patients.
 - 6) Develop an entire communications strategy that includes clinician, researcher, and front-desk roles and messaging. Patients are not the only ones who need communication deliverables—clinicians, researchers, and front-desk staff need to be involved, too, and on a personally fulfilling level (not just a ‘memo’ level.)
 - 7) Develop a stronger strategy around minority engagement. Foregoing the opportunity to tailor educational/engagement materials to specific minority populations could harm the NWBT, particularly considering how important and underrepresented minority specimens typically are in biomedical research.

Conclusion

Given local researchers’ difficulties in sourcing usable specimens, the NWBT is clearly poised to meet pressing research needs. This study focused on ways to support these research goals by indicating stakeholder views that can inform NWBT decisions. This study attempted to reach representatives of most stakeholder groups the NWBT will interface with in an attempt to help the NWBT attain its goals of improving local research and ethical consenting.

Tables

Table #1: Community Member Responses

Community member	Views on specimens	Terms + analogies	How to talk to patients	Quotes
Lab technician	They shouldn't be treated as much like an auto parts store	Encyclopedia, missing puzzle piece	NA	"I don't feel like we have the time to waste."
Biobanking project manager	We're not creating a repository, we're connecting samples to researchers	"Honest broker"	It's not possible to weed out all the 'no's' in the system for recontact	
CBPR researcher	-	-	Laughing and humanity should come first, research later – a lot happens during informal sharing	"We need to do whatever it is people do."
Community nurse/cancer patient	They're important, should be treated with respect	Trust	Keep it very simple and credit people with contributing to better outcomes	"Focus on the good and don't be too grisly."
Bioethicist	A lot of success has happened in relation to these cells	Colonization—the human body has become a frontier for exploration	Needs to be collaborative; social and economic goods should be shared to build trust	"We need to sit with and acknowledge emotions."

Table #2: Summary of Researcher/Clinician Responses

Tissue types researcher uses	Tissue sources	How specimens should be sourced	Quotes on Patient Involvement
Solid tumors, peripheral blood for immune response studies	Collects own (biopsies) Would talk to patients if asked.	In conjunction with industry – difficult when biobanks are developed only for their own purposes	“It doesn’t make a lot of sense for patients to hesitate in donating, when they’re using drugs developed from previous patients’ specimens.”
Multiple tissues for gene expression studies in cancer	Collaborate with three different clinicians, and with NY researchers	Would like to order specimens at UW; wants a central clinical research committee and IRB protocol specialist	“Patients are very motivated to donate, but the barrier is that there’s no easy entry route for them to donate tissues. ...We should talk about how restricting industry collaboration limits the development of cancer drugs patients need.”
Fetal tissues, anonymized tissues for gene expression	Fred Hutch and rotating pool of regular donors. UW uses 6 different ordering systems, which is way too complicated...“The thing I worry about here is the bureaucracy. A lot of places have a ‘can-do’ attitude, here is a ‘don’t-go’ attitude.”	Wants an easy centralized ordering system with visibility about what other studies are being done	“I think a lot of the concerns are overblown—some people will always decline to participate, but so many people are willing to help. They should know about the complications, but should also know that something going wrong is about as likely as a lightning strike.”
Oversees IRB approval for specimen requests	SCCA lacks in minority outreach, and the IRB struggles with adequate recruitment to studies		“Go straight to “What’s in it for me” with patients—they need to see the point of the consent form and not just have this ambiguous thing tucked in a clipboard for them to sign naively. ...Reach out more to minority communities.”
Colon cancer specimens for early cancer detection	Working with four different national agencies. Funding and regulation present barriers.	Universal consenting process and clean connections with clinical information	“Patients should get the message that it’s very important to science to accrue these biospecimens. They should also get a high-up view of logistics.”
Bone marrow and blood	Searching for new sources because preservation methods with older specimens are unsuitable for current research	A central place where other researchers’ work is visible for possible collaboration	“Emphasizing how funding cuts could hurt research, and how tissue contributions could help stratify risks. They should also know that scientists go through rigorous training and promise confidentiality.”

Blood and bone marrow	Solicits on own – says IRB requirements are a lot of work	Affordable annotated catalog and central database	“I emphasize that participating won’t affect their care in any way. ... Let people know they can really help. “That’s the most powerful emotion you can give anyone.” Tell narratives of satisfaction and of knowing you helped,”
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Table #3: Specimen Sourcing

	Locally	Non-local	Comments
Specimens Sourced	UW Neurogenetics UW Ovarian cancer deposit Children's	Case Western Vanderbilt GiCares Rochester National Disease Interchange Japan	<i>"We are trying to establish resources here at UW through some clinicians, but that's still in process."</i>
Type of Specimens	Rhabdomyosis sarcomas Brain tissues Mesoblastoma Neuroblastoma	Colon cancer Malignant cancer tumors	<i>"There's not good sources, we'd love to be able to tap into clinical sources."</i>

Table #4: Focus Group Responses

	C	D	K	M
Do you know any scientists personally?	-	-	Yes, many at Benaroya	No
What do you know about cancer research?	That there's lot of work going on trying to match up genetics with a person' care.		I'd like to know more—I suspect people are directly involved.	That stem cells exist, and that they do studies according to the scientific method...I don't like medicine—the whole thin scares me and freaks me out.
What do you know about body tissue samples in research?	They can be put into biobanks, frozen, and accessed for many years, but a lot of people don't have ways of collecting samples for research. I'm fearful giving up genetic material and don't know if it's really confidential.		I don't know that much. I have a level of ignorance about science in general. Are there giant rats involved? Monstrous things being created; that's the level of understanding people have about biotech.	No. Except for stem cells.
What term for this biorepository being developed do you prefer?	I like biobank because it's simple	Biorepository makes me feel like the tissue will be safe	Community biotrust/bioreserve	Biotrust sounds vague and like I can trust it
What about terms for tissue samples?	Sample	Sample is OK, but boring, donation freaks people out, gift is OK but vague	Combine sample and gift somehow: "Gift of a tissue sample"	Specimen sounds diabolical. Sample is unpleasant. Donation has the connotation of "OK, I'm doing something."
What name for our project is	I like SHARE (Seattle Health	NW Biotrust	I like the connotation of	NW Biotrust

most appealing?	And Research Exchange)		SHARE – NW Biotrust implies a biological corporate veil	
How would you like to be asked about donating your specimens?	A consultation with an expert is best. I could listen more in a kiosk and not be so nervous.	It's a bad idea to ask before going into surgery. The phone is nice and better than email, especially when contextualized.	A consultation with an expert is best. Or a kiosk might also be nice. Use as many educational tools as you can.	No preference. Human to human would be optimal.
Would you donate?	Yes, to get something positive out of a potentially bad situation. I understand that protections are in place.	Probably, but I would fear corporations doing things for profit. If I knew it could be patented I wouldn't.	I probably would—I don't think all genetic information should be free though. I'm interested in the bioethical implications.	Yes.

APPENDIX: NWBT SCRIPTS

SCRIPT A: RESEARCHER

1. What would you like people to know about what you do? Could you tell me how human tissue specimens matter in [or to] your research?
2. How do you source specimens?
3. What things help facilitate your sourcing and collection of specimens?
4. What barriers stand in your way for getting specimens?
5. What kinds of interactions do you have with clinicians over specimens for research?
6. What kinds of interactions do you have with patients over specimens for research?
7. Do you have any ideas on how to recruit specimen donors?
8. What do you think donors should know about the research process?
9. What factors do you think the NW BioTrust should consider for their design and for how they communicate?
10. What needs to happen for NW BioTrust to work for you?
11. Would you be willing to write a guest blog, post on a social networking site, give a talk at a community meeting, or otherwise be involved with informing donors (and the larger public) about your research?
12. Is there anything else you can think of that you would like to discuss (in regards to the Seattle NW BioTrust, to human specimens for research, etc.)?

SCRIPT B: CLINICIAN/PROVIDER

1. Could you tell me how human tissue specimens matter in [or to] your work?
2. How do you collect specimens?
3. What happens next to the specimens?
4. How do you discuss donating tissue to research causes with your patients (if you do)?
5. What questions and concerns do your patients typically have?
6. What encourages them to donate?
7. What discourages them?
8. What encourages you to collaborate with researchers?
9. What discourages you?
10. What kinds of interactions do you have with clinicians over specimens for research?
11. Do you have any ideas on how to recruit specimen donors?
12. What do you think donors should know about the research process?
13. What factors do you think the NW BioTrust should consider for their design and for how they communicate?

14. Does recruiting for/explaining tissue donation to your patients disrupt clinical work? [If so: What could lessen this disruption]?
15. What rewards do you perceive gaining in working to gain more tissues specimens?
16. What has to happen for NW BioTrust to work for you?
17. Would you be willing to write a guest blog, post on a social networking site, give a talk at a community meeting, or otherwise be involved with informing donors (and the larger public) about your work?
18. Is there anything else you can think of that you would like to discuss (in regards to the NW BioTrust, to human specimens for research, etc.)?

SCRIPT C: FRONT DESK PROFESSIONAL

1. Please describe a normal CODI check-in procedure to me.
2. What is an average amount of time patients spend in the waiting room?
3. What questions or objections do patients normally have? (Please elaborate, including % of patients w/ comments, etc.)
4. Would adding another consent form, of the kind we're considering for the NW BioTrust, prove burdensome?
5. If so, how might this burden be lightened?
6. What might be exciting to you (or to patients) about the NW BioTrust?
7. How could we make the NW BioTrust work for you?
8. What do you think of the NW BioTrust including patient education materials (hand-outs, brochures, etc.)
9. What do you think of the NW BioTrust including patient mementos (certificates, postcards, etc.)
10. What are your thoughts on research, and on patients' connections to research conducted at SCCA?
11. Where do you see yourself in SCCA's mission?
12. Is there anything else you can think of that you would like to discuss (in regards to the NW BioTrust, to human specimens for research, etc.)?

SCRIPT D: PATIENT

1. What do you know about research and SCCA?
2. What do you think about your own role in research at the SCCA?
3. [Explain NW BioTrust]. To get your consent, we'd need to add another form to your check-in routine. What would this mean to you?
4. Do you think you would have questions about NW BioTrust's goals and procedures? [If so, please elaborate].
5. What would appeal to you, in terms of education, to tell you more about NW BioTrust?

6. What appeals to you, or seems puzzling, about NW BioTrust's goals and procedures?
7. Would you like research updates?
8. Would you like to see an accompanying website?
9. Would you like the chance to interact with researchers directly?
10. When would you want to find out more about NW BioTrust (in the waiting room, via email later, etc.)?
11. What would make NW BioTrust work for you?
12. Which of these materials do you prefer? [Show pamphlets #1 and #2, Handout #1, Postcard Sets #1, #2, #3] Why?

Chapter 2: Interpersonal and institutional trust considerations when conducting research within health learning systems

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Introduction

Trust is clearly important within patient-provider relationships—the kind of trust modeled in this key health care relationship, I argue, is worth considering when attempting to build patient or participant trust in researchers or institutions. In this paper I explore components of trust and the utility and ethics of leveraging trust-based relationships when seeking to conduct research that draws from or is affiliated with clinical health care systems. I reference results from: 1) the 2014 Attitudes about the Ethics of Research on Medical Practices study, which was devoted in part to investigating the relationship of trust in brokering relationships favorable to research within health learning systems (Kelley et al, work in progress), and 2) results from the development of the Northwest BioTrust, a Pacific Northwest biorespository resource (reported in Chapter 1; publication pending.)

Background: Trust, Healthcare Systems, and Research

As the disciplines of genomics, large data analysis, bioinformatics, and biobanking advance, it becomes possible to integrate research approaches with clinical care in increasingly complex and comprehensive ways intended to better serve both individuals and entire populations. In the process, however, the tension between researcher and provider roles, respectively, in advocating for overall population needs versus immediate patient needs tightens. Research-related consent procedures are still separate from treatment procedures, however, and the need to obtain informed consent from patients in settings that blend care with research presents unique ethics and policy challenges in which trust plays both functional and ethical roles, and as the need to develop policies around consent for research conducted in clinical settings sharpens, it is necessary to understand how patient trust in care providers, researchers, and institutions operates.

Research and health system partnerships

Systematic comparative effectiveness research, like that conducted within research on medical practices offers a way to standardize clinical care, eliminate many of the confounders and subjective elements found in clinical decision-making, and track overall patterns to eventually discover more effective and efficient treatments (Kim and Miller 2014). The availability of large data sets from electronic healthcare records, combined with policy-driven mandates to make evidence-based health care more efficient and effective, encourages the blending of research with clinical care.

These practices, containing as they do possible tensions between individually-based and population-based treatment goals could be linked to additional risks patient might experience beyond the risks of standard care (Kass et al. 2013). Trust-based relationships between patients and physicians helps mediate risk and medical decision-making (Hall et al. 2002), and in the context of health learning systems, it would be helpful to know how trust could assist physicians, researchers, and patients navigate decisions about patient participation in research on medical practices. The decision delivered in response to the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) study by the Office of Human Research Protection (OHRP) and ensuing discussion about the study's ethics and consenting practices particularly underscores the need to understand trust in this developing field (Macklin, Shepherd, and Einstein 2013; Magnus and Caplan 2013; Magnus 2013; Wilfond 2013).

The research conducted during SUPPORT entailed randomizing premature infants to different oxygen saturation levels, all of which were considered acceptable within the range of standard of care. SUPPORT researchers deemed the trial essential to tighten the target range of blood oxygenation levels optimally, since current standard of care practice levels could result in infant deaths, if oxygenation levels were too low, or, alternatively, in retinopathy for infants treated with overly high oxygenation levels. Since the ideally targeted

range was not known, researchers used randomization to standard of care levels. OHRP notified involved institutions that SUPPORT was not fulfilling regulatory requirements for informed consent, due to failing to disclose enough information about the research design and attendant risks—even though the levels of oxygenation into which infants were randomized fell within the spectrum of standard of care, OHRP judged the introduction of randomization to introduce certain foreseeable risks that should have been more clearly acknowledged and explained as such. SUPPORT researchers responded with an appeal published in the *New England Journal of Medicine* (Wilfond, et al, 2013), and several of the signatories have since engaged in research on patient perceptions of risk related to research on medical practices.

Trust has emerged as an important theme during this research, particularly the theme of trust situated within patient-provider relationships.

Trust and the patient-provider relationship

Trust performs several functional roles within the patient-physician relationship—without trust, in fact, a truly operational patient-physician relationship is impossible, which positions trust as a fulcrum upon which a socially responsible medical system rests (Jones and Barry 2011). Treatment adherence, openness during consultations, physician loyalty, and levels of engagement are all impacted by trust (Hall et al. 2002; Ozawa and Sripad 2013a; Helliwell and Wang 2011). Trust gives patients a short-cut to place confidence in physician decisions without needing to question each one at length, lubricates team functions and helps patients interface with related researchers and other entities, and helps mitigate perceived and actual medical risks.

Since public trust and mistrust can “bleed” from physicians to related medical entities and to researchers, it is vital for physicians to place a priority on positive clinical encounters sustained over time with patients and for researchers to recognize and honor the risk-mitigating functionality of trust (Rothstein 2010). By

its very nature, trust implies taking action despite possessing insufficient information for complete assurance. Trust, in other words, is a way to navigate risk. Trust is a successful strategy only when trusted entities uphold expectations placed upon them, however, and medical systems are no exception (Resnik, Patrone, and Peddada 2011).

Strong patient-physician relationships let patients more easily navigate sensitive, “riskier” situations—minority patients, for example, may regard clinical research with heightened degrees of distrust unless physicians can adequately demonstrate sensitivity and appropriate responses to these patients’ concerns that alleviates the mistrust and allows medically-affiliated research to proceed (Durant et al. 2011). Measures of trust in medical settings tend to focus on interpersonal factors over inter-institutional factors (Ozawa and Sripad 2013b), but patients still cite institutional trustworthiness as a primary factor in making choices about where to seek medical care.

King’s work in examining physician’s obligations when discharging the duties of both care provider and researcher are instructional, and point to the importance of providers thoughtfully inhabiting both roles—for these authors, the fiduciary model is a useful guide to how patients and providers can relate while honoring both care and research obligations (King and Churchill 2008). King and Churchill go on to explore patient impressions when dealing with providers who dually occupy the roles of provider and researcher; they find that patients expect researchers to enter care-based relationships but do not simultaneously tend to confuse research activities with care-giving. Patients are apparently able to tease apart the complexities of relationships they may widely encounter within health learning systems, though the relationships themselves, whether care or research-directed, are still grounded in patients’ minds (and sometimes in providers’/researchers’ as well) in care based on relationships instead of contracts (Easter et al. 2006). This centering of trust in relational dynamics instead of in the mechanics of the consent form and attendant information

indicates an important pressure point within research ethics: while regulatory bodies in research ethics have often sought to earn or prove trustworthiness through contractual interactions, patients identify trustworthiness in the context of healthy patient-provider relationships. In other words, consent forms may not substitute for readily apparent care.

To learn more about patient beliefs and preferences regarding research on medical practices, including how trust functions within clinical spaces and might function within health learning systems, we conducted small group interviews and focus groups for the first phase of our mixed-methods study on attitudes toward the ethics of research on medical practices.

Methods: We completed data collection at Seattle Children’s, Stanford University, and the University of Washington. During the study we conducted three focus groups with a total of 22 Institutional Review Board (IRB) members, and recruited a total of 53 participants spread across 2 small group interviews and 3 patient focus groups and 5 focus groups or small group interviews of parents of pediatric patients. All participants were recruited from cardiology and nephrology clinics associated with the University of Washington Medical Center, from Seattle Children’s Hospital, and from clinics associated with Stanford. We used interview and focus group results to develop surveys we administered to 1500 IRB specialists and 3000 patients. We recruited IRB members through email; patients were recruited by a combination of email sent to an academic health system’s research registry and by in-person recruiting conducted at adult and pediatric cardiac and nephrology clinics. All focus group and small group interview participants (or, in the case of the pediatric-oriented focus groups, participants’ children) had been seen in associated clinics at least twice in the preceding calendar year.

For both IRB and patient focus groups we appointed a senior research team member as the head moderator. Junior research team members sat in as note-takers and general observers. Moderators across all focus group sites used

identical semi-structured focus group guides, respectively, for IRB and for patient focus groups. During the patient focus groups we showed participants three animated informational videos illustrating concepts about research on medical practice.

Our data was uploaded into the analytic software program Dedoose. We initially generated codes inductively via group readings, using a subset of data for verification; our code tree was subsequently built via successive iterations of combined *in vivo* and *a priori* coding. Modified grounded theory informed our hypothesis generation and data analysis (Kelley 2014). At least one primary and one secondary coder independently coded each transcript.

Results

IRB and patient focus group and interview data was organized around themes, reported elsewhere. In brief, participants reflected a difficulty in understanding research on routine medical practice. Key findings included identifying a central tension in research and medical practice between attending to the needs of a population or an individual. Additionally, relational elements were central to participant considerations throughout the research process from consent, study design, and participant engagement.

Trust was such a prominent emergent theme in our data we have delved more deeply into it and here analyze our data for sub-themes pertaining to the larger themes of trust, autonomy, shared decision-making, and patient-provider relationships.

1. IRB responses regarding trust:

IRB members expressed caution about using physicians to recruit research participants in health learning systems. They did not take patients' trust in their health care providers for granted and expressed concerns about coercion.

The investigator says where are you going to get the people? Well, from my practice. And there's automatically some, I won't say coercion, but some incentives on the part of the patient to follow the doctor's instructions. The doctor says, "I've got this study, would you like to be in it?" You're going to be predisposed to say yes, and that's a subtle form of coercion, although it's perfectly understandable.

IRB Focus Group Participant

There was a time when people trusted their doctors, or so I've been told. I think it was before my time.

IRB Focus Group Participant

Patients, IRB members thought, are now more likely to seek additional information, implying that the patient-provider relationship could not help patients make decisions about participating in research based on their providers' advice or recruitment.

But the problem is society evolves so much. I know that people have made the comment that people just trust their doctors implicitly, and in the old days when my parents - when we had physicians, you did exactly what the doctor told you and you didn't question it, whereas now we get second opinions. I know, as I said for myself, I'm a little bit more of an advocate and I ask "why?" And it seems like my peers, my colleagues in the community that I'm affiliated with, they do it too. So you're kind of - it's almost a moving target as you try to make decisions for the public but ask their opinion, when the public opinion is also changing.

IRB Focus Group Participant

What trust there could be, IRB members implied, depended on physician openness and on open acknowledgement about any research proceeding.

As I define ethics, one component of it is surprise. Don't surprise me. If we talked and it might happen, okay, I went into it. But if you say nothing and it happens, we've got a problem when you could have told me.

IRB Focus Group Participant

Oversight that incorporates representatives of patient communities was thought important and important for preserving institutional trust.

At least if you had community input in studies, and I agree, when they're necessary, you preserve that public trust and let them know that at least you guys also had input on what we did moving forward, and that globally does have a positive effect.

IRB Focus Group Participant

2. Patient responses regarding trust:

Trust in chosen providers helps patients navigate vulnerability

Patients were generally aware of their vulnerabilities within the medical system and described often having to confront disparities or uncertainties in knowledge, power dynamics, and financial obligations. To help mitigate these vulnerabilities they exercise caution in carefully selecting those providers that seem most professionally and empathically equipped to prove worthy of their trust. By researching doctors' reputations and proof of competency ahead of time and by expressing preferences for doctors who are skilled at communication and at demonstrating care as additional indices of trustworthiness, patients begin to extend trust based on measures of reliability.

I feel that typically I spend the time choosing my doctors in advance so that I trust them. So if they lead me down the path of you know 'You need to take this drug for this condition,' then I trust their decision and I don't really question how they come to it... I've already done the research on 'How much education have they had? Do they stay on top of [the] latest research?' and that sort of thing, and that's one of the things I look at, and so I typically, I trust the doctors that I'm seeing.

Patient Focus Group Participant

[W]hen you personalize things, it makes us as parents feel more engaged towards you and more entrusting, and I think that's always been a question in the back of my mind is like I don't understand how doctors can be doctors here, because they see so many bad things and such on a

generalized scale, and it's like but they still care about you and they still say 'We're gonna help you,' and I would be lost without that.

Patient Focus Group Participant

Patient see trust-building as the responsibility of both parties

Patients recognized their own role in forming trustworthy relationships and their own responsibilities in both carefully selecting a provider and in doing supplementary research to inform their own medical decision-making. They were not trying to shift the complete burden of proving trustworthiness onto the provider, but did see trust-building as collaborative and did recognize the unique knowledge about their own bodies they could bring to decision-making.

I basically want to add, that's basically what I was gonna say, but I think it's two-fold. Initially, like he said, when you go to the doc, you put all your faith and trust in him, but I think it's also incumbent upon us as patients to learn as much as we possibly can so as we move forward, we will have the knowledge. We know how our bodies feel.

Patient Focus Group Participant

Expressing care in patient-provider relationships matters for establishing trust that extends to research

Providers with low empathic abilities, with short attention spans, or with overly packed schedules all convey untrustworthiness, or at least reluctance and an inability to reassure patients. Patients knew that providers often carry heavy case loads and balance multiple obligations, but patients were also less willing to trust providers who could not seem to prioritize individual patient interests while balancing these competing obligations. Patients expected providers to actively express care and to offer treatment with a certain degree of warmth and devotion to patient interests.

Well I mean in my case, I pick between a lot of doctors. I try to interview them. I mean everything I do, I mean I'm not a doctor. I have doctors in the family and I can read and I can study, right? But it boils down to every

doctor that I pick, I never really necessarily pick the smartest and the brightest doctor. I pick the one that was most willing to learn from another doctor and the one that was willing to communicate and share with me what it was and that they have truly the heart to take care of your kid. So the first doctor, the geneticist that I had, I fired her the moment that she said 'Oh great, now I have you because it was just...' It was heartless. It was 'Oh now I have research. I don't care about your kid.' I mean she literally desensitized the whole situation, right? By the time that somebody puts you in a trial like that that our kids are so bad that I don't think anybody will care in the sense that we all want the kid to live, right? ... So it depends on the relationship I have with the doctor I'm working with. If I think he's a jackass, I will say so, literally. If they tell me from their heart, 'I think this is good for him, what we need to do,' then I'll say yes.

Patient Focus Group Participant

Patients can trust physicians because of their understanding of how medicine is practiced within the matrix of a team

Patients express trust not only in individual providers, but in individual providers as members of larger medical teams and as adherents to the larger, relatively codified practice of medicine. Individual providers expand trustworthiness by transparently consulting with other providers and by upholding expectations patients have of overall medical practice.

Once a doctor comes to me and says 'Okay, this is what we want to do. We want to take A, B, C. After I've asked the questions and after I've been satisfied with the answers that he's given me as to why he's prescribing this medication for me, I feel comfortable with his decision because I understand that he's a part of the team, and if he's prescribing this medication to me, then the team has given him the option saying 'Hey. This is the deal. All of these will work for your patient. You can give him any of these. Now you choose the one based on his history and the other factors which is gonna be best for him,' but I know that his team, the people who actually made the decision for the medication, I know that they have done the research and that he is intelligent enough and wise enough to make a tangible decision to choose the right drug in conjunction with me, choose the right medication for me. So in terms of somebody else being involved with that procedure, it doesn't bother me a bit, as long as we get it right.'

Patient Focus Group Participant

Trust established in medical teams can extend to researchers

When research is added to clinical settings within health learning systems, patients can extend trust to specific researchers as well as the aims and practices of science itself, due to their understanding of how medical practice works. Because patients trust their doctors and medical teams, they trust researchers being added to the team as well.

I would defer to the doctor and researcher because of the breadth of medicine. I think that...I'm repeating myself, might be interfering if you say, "Hold on. Stop. Wait a minute. If you get all the info, please." I would just let them make the call either way."

Patient Focus Group Participant

Demonstrating care is important for building trust in researchers

Patients were more apt to distrust individual researchers than they were individual care providers, due to the perception that researchers lack empathy, are "cold," or have even more potentially troubling conflicts of interest and fewer enforced obligations to treat patients with respect for individual patient needs, preferences, and treatment outcomes than do medical providers. Researchers, participants thought, typically possess more status and power than do participants, without having the "skin in the game" clinical staff do and without the checks and balances of personal relationships to temper their work.

They know our child. They know us. We've been in the trenches with him. I mean again, we've been here for... And Robert [the name of the character of the researcher in our videos] is just (no offense) Robert, and Robert's just some guy off the street in a UW trial, or you know what I mean, but it's like there's no vested interest for Robert to convey anything. He's just a very neutral, very great person, whereas the doctor is...Trusted.

Patient Focus Group Participant

“...because the researcher is so focused on the research, they may have more difficulty even listening to what side effects or other potential problems a patient may be having that would necessitate change.”

Patient Focus Group Participant

Trust is useful in clinical spaces, but patients do not trust blindly

Depending on their personal preferences, patients feel comfortable both within a shared decision-making model or within the traditional model of deferring to a provider’s judgment as long as trust is present. If the provider makes a judgment error or seems otherwise untrustworthy, however, patients are able to advocate for their own interests. Healthy patient-provider relationships and transparency in communication help patients confidently express their own preferences and feel safe enough to decline research participation opportunities.

So we have a greater sensitivity perhaps because of that, where things have gone wrong in ways that we never perhaps anticipated and medications that are supposed to help us have gone horribly wrong so the relationship with your physician, the questions they ask you, what they know about you, what you share with them, I think is a very important relationship and knowing the full extent of that relationship, developing that trust, is something that’s very important and that if things are happening without your knowledge, like you’re being put into a study without your knowledge or a random drug study without your knowledge, then I would object to that.

Patient Focus Group Participant

Patients are willing to question doctors’ decisions if necessary

Though patients respect providers’ decisions, they are willing to advocate on their own behalf, particularly when they suspect a provider might not be attentive enough to their interests or might be ignorant of or indifferent to a patient’s special concerns.

With my doctors, they’ve given me medications and it made me not feel good and I immediately called and said ‘Hey. Something’s not right,’ and they changed the dosage, but that’s only because not only because of the

way that I feel. I also read and I ask questions. By me being a minority, a Black male, I know that there are different medications that will help me more so say than say an Asian or Caucasian, and I ask. I say 'Have there been any studies done on this particular blood pressure medication that's geared towards minorities?' and he said 'Yes.' I said 'Well which one do you think will work best for me?' So I say we as patients, we have to ask, and if we ask, as they're saying, as we move forward, then we'll have the knowledge and we'll be able to say 'That's not working.' And if you have a doctor and you tell him that the medication is making you sick or you don't feel good and he continues or she continues to try to keep you on that medication, that's when you have a problem.

Patient Focus Group Participant

Commercial interests can introduce mistrust

And even though patients realized providers must make a living, they regarded provider ties with insurance companies and pharmaceutical companies, for example, with deep suspicion because these ties appear to potentially sully or threaten the primacy of the patient-provider relationship and could compromise a provider's dedication to his or her patient's wellbeing.

I think it's a combination. I have a good group of doctors and I have no complaint, but I pretty much agree with what everybody say, but maybe put it in a capsule, I think it's a combination of the insurance. I think it's a combination of tests. I think it's a combination of experience. I think it's a combination of all three things, but if you have a good doctor, he put all that aside and put your best interest at heart, and unfortunately all doctors aren't that way. I'm not saying they're not ethical, but I'm saying sometimes their decisions are driven by economics and finances.

Patient Focus Group Participant

Patients trust reputable institutions, and this trustworthiness can extend to research conducted at these institutions

Patients deliberately seek out the best care institutions and are more willing to trust decisions made at these institutions. This institutional trust brokers patient willingness to participate in research.

I have a lot of confidence in UW, so I don't really worry about it. I came from a different hospital before, and UW is a much better hospital, and the other hospital does the same thing, and then I also did research before my transplant and UW is one of the best and I know that they are very strict about the doctors that they hire, so I just have a lot of confidence in UW itself and my doctors. I'm not really too concerned. I know that if I have a problem with a medication that all I have to do is call and they'll change it. So I haven't had any issues with UW.

Patient Focus Group Participant

...and I'm not kidding you. I passed Evergreen and I passed Bellevue. I passed good hospitals to come here because the fact that I trust them, because if I go anywhere else, they'll say 'We're just not quite sure. We're gonna send you to Children's,' and it's like you could've gone there anyway, and it's like the best of the best are here. There's people that come from all over the world here.

Patient Focus Group Participant

....I come here because my feeling is that it's a teaching university and it's more research oriented, and so my feeling is that the doctors are more up to date on the latest research on techniques and drugs, and I just have a feeling that I will get more up to date, latest service at [Medical Center] than if I went to anyplace else.

Patient Focus Group Participant

Discussion

Understanding trust in medical systems is important because medical systems by their very design place most patients in a position of vulnerability trust can mediate. Hall and colleagues define trust in a medical system as “the optimistic acceptance of a vulnerable situation in which the truster believes the trustee will care for the truster’s interests” (Hall et al. 2002). Patients do not usually possess as much specialized knowledge or power as their providers, and are thus expected to relinquish certain aspects of personal autonomy in acknowledgment of a clinician’s superior judgment. Culturally, patients have also been encouraged to trust clinicians, due to expectations that the clinician will be both impartial and well-meaning—this vulnerability combined with treatment expectations could potentially confuse trust with dependency (Gilson 2003). Our IRB respondents demonstrated concern about these possibilities, though patients themselves,

while they did acknowledge vulnerability, did not seem to fear undue influence from physicians during the decision-making process, particularly when they remained confident in their own ability to double-check physicians' assessments. Rather, if physicians appeared trustworthy in care relationships, patients appeared willing to trust them in research-related settings as well.

Our results confirm how patients strategically rely on interpersonal and institutional trust to assist them in making decisions within clinical settings, including decisions regarding their level of participation in research. Within healthcare, trust works both interpersonally and across organizations—though measurable in different ways, both forms of trust are influential, and both seem linked to transparency (Jones and Barry 2011).

A sustained set of positive interactions between doctors and between patients and medical centers builds this sense of trust, with each interaction being a chance to fulfill or betray the expectations upon which trust is grounded. As our patient participants testified, providers specifically build trust by creating emotional bonds, by demonstrating vested interest in the patient's wellbeing, and by practicing transparent communication, which aligns with the literature to date (Gilson 2003)

Importantly, and relevant to the data presented in Chapter 1, this trust does not automatically extend to researchers allying themselves with clinicians. Participants noted that researchers often do not understand what it means to be a patient and to grapple with concerns a patient or parent of a patient must face daily. Researchers were perceived as being "beyond the clinical pale": they do not have the "skin in the game" clinical staff do and thereby lack the checks and balances of personal relationships to temper their work. Participants realize they have personal needs as patients and feared research methodologies that might overlook these unique characteristics and thereby result in unfavorable treatments. It was difficult, in other words, for patients to conceive of researchers

successfully viewing them as individuals with individual needs, which became another source of mistrust.

Our findings imply that providers, if learning health systems are to operate as well as they could, will bear much of the transactional weight of transitioning traditional clinical trust to trust in researchers and in research itself. If providers were brought more intimately into the process of brokering research, participants indicated they would be less likely to feel used, since (within healthy relationships) they trust that their doctors truly desire their own wellbeing. Participants believed that researchers would not have such a developed stake in patients' health, and since participants had not already established personal relationships with researchers, they were apt to regard researchers as "cold" and as lacking investment in patient outcomes.

While providers may not want to adopt the role of brokering trust in research, research endeavors aimed at improving patient outcomes could suffer if they do not. Successful compromises in consenting practices that build comprehensive informed consent into clinical environments have been achieved before (Yamada et al. 2013), indicating that even though providers may have legitimate objections to being asked to assume the burden of administering consent, workable solutions can be reached. Still, the demands of clinical practice and the difficulties of subsuming research practices into clinical environments should not be underestimated (Capron 2013).

Another compromise could be to embed community advisors in clinical settings who can interact more extensively with patients, who can help patients navigate consents and research concepts, and who can serve as a liaison maintaining ties between medical team members, researchers, and patients. Alternatively, our participants expressed some interest in community members taking an active role in research study oversight, not necessarily by serving on IRB boards alone, but also by being invited to participate at the study-design level, or otherwise gain

access and meaningful oversight of ongoing research that involves community members.

Researchers must not blindly assume they can rely upon these relationships alone, however. While researchers' work stands to benefit from judicious collaboration with providers patients find trustworthy, researchers also have an opportunity to normalize the research-treatment bond being created in health learning systems. As our results demonstrate, patients value the research conducted within reputable institutions and are willing to support this research—their trust simply does not extend to researchers themselves, since patients have not had many opportunities to experience the kind of personal encounters with researchers they have with providers. The factors giving potential participants pause could plausibly be overcome not only via providers, but also by researchers willing to demonstrate their good faith and their desire to build their own trust-based relationships with patients.

Both physicians and researchers have a stake in improving patient/participant trust in both medical team members and researchers—researchers, particularly, can benefit from emulating the kinds of trust relationships successful medical care team members already enjoy with patients. To demonstrate trustworthiness, researchers should consider emulating physicians in demonstrating sincere care and in communicating transparently. To aid in establishing trustworthiness, a provider must become familiar with a patient's needs and preferences—the provider must see through the patient's eyes and be able to incorporate patient priorities into care decisions in a way that demonstrates empathy as well as professionalism. Once a provider has adequately proven that he or she can accomplish this, the patient, particularly if she or he is from a marginalized group, may relax vigilance based on fear or mistrust and can progress to feeling confident in ongoing collaborative clinical decision-making (McDonald et al. 2012) To balance disparities in degrees of power and vulnerability, medical providers as a whole have a vested interest in being trust-worthy, particularly since trustworthy medical systems do contribute to overall social good. Patient

vulnerability, then, must be shifted from strictly contractual trust to a relational trust supported by empathy and transparency (Misztal 1996:68; Gilson, 2003).

Researchers can establish transparency by supporting clinical staff in seeking consent clearly and ethically, by communicating the specifics of their research plans in channels easily accessible by the publics they seek to involve in their work, and by demonstrating gratitude for participant contributions concretely through thank-you cards, community engagement events, scholarship funds, or similar practices. Researchers would also do well to incorporate patient advisors into study design meetings from early on, and could further demonstrate transparency by posting research plans in easily accessible public fora (including bus advertisements, an online presence, journal articles not secured behind a paywall) and by issuing regular update so interested participants can track along. Researchers could also seek opportunities to build more personal relationships by helping set up patient information-sharing groups (something our focus groups explicitly requested), and by conducting the kind of qualitative research that brings them face-to-face with participants so that both may benefit from personal interactions.

Consent forms present another opportunity for researchers to push beyond legal requirements and instead seek more meaningful engagement. Participants are not satisfied to limit their understanding of research being done with their specimens and medical records to consent forms typically signed cursorily and without the opportunity to easily ask further questions or receive regular updates—giving participants a chance to have their questions answered through a dialogue would demonstrate respect for these preferences and would accord with previously documented patient views (King and Churchill 2008).

Consent forms at the present may be discharging a regulatory obligation and protecting institutions from accusations of malpractice, but they are being asked to shoulder unrealistic expectations regarding what they can actually accomplish. The consent form can act as a public declaration of trust, but only after patients

have developed trusting relationships with involved providers and institutions. Our participants reminded us that they often do sign consent forms without really reading them, due to their trust in the institutions they had sought out. If trust is indeed at play, the consent form itself may be doing very little of the ethical “work” of consent, and researchers may want to consider the plausibility of requesting a waiver of documentation of consent.

Finally, financial demonstrations related to care also matter to our participants. While they expressed concern about potential commercial ties in clinical spaces (i.e., insurance companies’ involvement), Steinsbekk et al. have shown how patients, with sufficient explanation, can reconcile commercial involvement with the goals of modern medicine. Humanity remains the linch-pin: as long as participants feel cared about and respected in both clinical care and in research, they are willing to vouchsafe their trust in general (Steinsbekk et al. 2013).

While it may be impracticable to return portions of eventual profits to individual participants, other forms of giving back could be helpful to show how researchers are concretely supporting patient outcomes by showcasing equipment for patient populations, by holding events that benefit participants, or by donating to community causes like a scholarship fund. Researchers need to show how they are distinct from doctors in training and goals, yet are likewise invested in patient care and in contributing to healthy communities.

Concerns about data security and confidentiality have been well-documented among patient populations, and have been cited as a consideration holding patients back from donating to biobanks, for example (Rahm et al. 2013). In our study, despite confidentiality and data security being mentioned, participants did not find these persuasive reasons to mistrust clinical care and research.

Our participants were quite open, in fact, to research involving medical records review, and in fact expressed surprise that such research was not automatically ongoing. They assumed that by receiving care, they were also indicating consent

for their providers to share their (de-identified) medical information with other providers and researchers in hopes of finding better individual and population-wide treatments. We contend that this openness is due again largely to trust, not necessarily trust vouchsafed in individual providers, but trust in an ongoing process of seeking ever-improving patient-based care. Though participants might not formally recognize this as systematic research, they did express regret and frustration, were these records and data sources to be under-utilized—this parallels the frustration Cadigan and colleagues have commented on prospective biobank donors whose contributions may be underused (Cadigan et al. 2013). Our patient participants expressed little reservation about possible privacy concerns—some thought HIPAA privacy protections too restrictive, in fact, and most thought keeping their information completely private was a futile mission to begin with. Better, their attitude was, to risk a data leak by sharing records for the common good than to overprotect records and actually cause greater harm to patient communities by neglecting to conduct research that could benefit these communities.

Limitations

Our findings are preliminary, and are subject to limitations. The small number of participants could limit the generalizability of our results, and the manner of recruitment could have introduced systematic bias. Recruiting patients only within cardiology and nephrology clinics could also have introduced bias. We will be positioned to better understand if these findings are representative or not once we complete analysis of surveys administered to 601 IRB members and to 3000 patients; those surveys were based on our focus group analysis.

Conclusion

Earning trust might be as difficult as defining trust. However, neither task is impossible. Trust is reliably built by valuing participant input, by honoring both contractual and care-based aspects of the researcher-participant relationship, by

seeking genuine partnership founded on personal relationships, by fostering clear, practical, effective communications, by appointing dependable monitoring bodies, by actively soliciting ongoing participant feedback, and by regularly taking trust's temperature (Beskow and Dean 2008). Trust in clinical and research spaces is developed along multiple axes, though clear communication and personal, empathy-based relationships are important in every axis. Trust helps clinicians perform their work well, helps validate affiliated researchers, and helps relieve, though not obviate, the weight of patient responsibilities.

Chapter 3: Reflections on Consent, Trust-Building, and Relational Autonomy in Biomedical Spaces

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Introduction

We know researchers are trusted far less than care providers are, and we know that public trust in doctors could be waning, too (Master et al. 2013a; Tauber 2003). This “crisis of trust” concerns researchers and clinicians who work together at the intersections of science and medicine (Hoeyer 2012), such as in health learning systems, where research is increasingly being systematically combined with ongoing clinical care, typically using comparative effectiveness research (CER) approaches. Developing fields that require public support and informed consent, like health learning systems or biobanking, might be particularly vulnerable to lapses in trust (Goddard et al. 2009). Trust plays a profound role in potential participants’ decisions (Cadigan et al. 2013), and, given the developing tension in health learning systems and biobanking between individualized medicine and research benefiting entire populations, trust is understandably valuable, yet difficult to pin down. Is this deficit-based framing of the issue an ominous warning peal, or simply an overly pessimistic interpretation?

As Hoeyer points out, researchers have never been held in the highest regard, but there are other explanations for patients’ apparent lack of trust of them, most notably that researchers are obligated by the nature of their work and training to generalizable results, not to specifically promote a specific individual’s health and wellbeing. The worried contemplation being invested in the current trust “crisis” could be attributable more to the public’s ignorance than to public opposition to being asked to demonstrate trust. Biobanks, health learning systems, and other instances in which research goals dovetail with medical environments are fairly new, after all—their visibility is still low, and the public has had little precedence for trusting them (Hoeyer 2012). Given mistrust arising from past mistakes, patients could readily transfer this mistrust to these new incarnations of research,

should they discover that practices they oppose are being carried out, with or without their consent.

Health learning systems are so relatively new, policy makers are still working out advisable ways of educating patients, obtaining consent from them, and considering the risks to which they may be subjected. Biobanking literature amply documents how betrayals of public expectations regarding researcher conduct, such as the Havasupai case, continue to feed patients' mistrust-based reluctance to participate in research (Cochran et al. 2008). The public's trust is necessary for research success, (Critchley et al. 2012), yet low accountability, lack of oversight, muddy policies on return of results, and inadequate consent forms all demonstrably undermine trust alongside betrayals (Anderson and Solomon 2013).

But trying to rescue trust and reconstitute it, as though it is indeed in crisis, does trust an injustice we could better address by examining how different stakeholders conceive of trust, the work it accomplishes, and the ethical considerations it entails. Trust, I hold, comes down not to a dearth of meaning well but to a set of systematic misunderstandings.

Before addressing these misunderstandings I will briefly cover where we stand on defining and understanding trust in medical landscapes today.

Trust within the changing medical care landscape

Trust in clinical environments was traditionally more localized to the patient-provider relationship, when care providers assumed responsibility for gaining patients' trust, sometimes even through patriarchal tactics based on knowledge the provider had gained over time about individual patients—this responsibility was based on care-based relationships and was meant to leverage providers' knowledge for patient good. Care providers did occasionally conduct research on

patients, though generally without today's protective consent forms (Miller 2014). In these cases, however, the provider had still generally had at least some time spent face-to-face with their patients; the provider could often practice simultaneously as both a doctor and a researcher. Adding more generalized research methodologies to research practices, however, chisels away at the possibility of conducting research only with 'known' patients, decreases the likelihood that care providers will hold both clinical and research-based roles, and encourages shifts in clinical practice and the kind of relationships providers and researchers can, both independently and jointly, develop with patients and participants.

The pre-Belmont days of the physician operating independently as both researcher and doctor had their place, but today's large-scale data sets and data sharing capacities call for very systematic approaches to research and medical practice. Just as research on the ethics of medical practice is attempting to remove the subjectivity inherent in current medical practice by promoting research practices like randomization of standard care, subjectivity in determining the ethical balances between patient and population also needs to be minimized (Joffe and Miller 2008; Largent, Joffe, and Miller 2013).

The feasibility of assembling and analyzing large data sets from patient populations, however, does not imply it is as possible to earn the patient trust and consent ethically necessary to drive these large-scale research approaches. 'Big data' shifts analysis toward depersonalized analysis, but without necessarily implying that we can dispense with the personal relationship-building and clinical consent that often characterizes the patient-physician dynamic. "Bedside manner" is quite important in the practice of medicine, and perhaps this implies that, particularly when medical practice is combined with research, that research needs to develop its own "bedside manner," or at least learn how to adequately enter the clinical space as part of a care-based relationship partnering with individual providers or, potentially, with entire institutions instead of on its own depersonalized terms.

Multiple measures of trust have been developed to help analyze trust's function and how to build trust within clinical spaces.

Trust measurements within relational ethics

Trust is grounded in measurable elements. For example, 45 measures of trust already exist in the United States to weigh trust in different areas of health research (Ozawa and Sripad 2013b). When asked about their specific levels of trust in different health-related entities, 71% of cancer patient respondents surveyed had “a great deal of trust” in doctors, 63% in hospitals, and 40% in university researchers receiving government funding (Master et al. 2013a). The stair-step progression of trust is easy to perceive here, and indicates what I believe is the primacy of personal relationships in forming the kind of trust that can be translated to include research endeavors in clinical spaces: the more familiarity participants have with a particular system and the more they can couch their decision in terms of relationships they can understand and individuals they can relate to, the more willing they are to extend trust. Master and colleagues, for example, document how cancer patients typically show higher levels of organizationally-based trust (Master et al. 2013a), which could be due to their increased exposure to these environments and reliance upon them.

Given all these measures and our attempts to understand how different people conceptualize trust, we would be well-served by settling on a universal definition of it.

Trust does not have a universal meaning

Trust is famously difficult to delineate precisely. Its very vagueness permits individual interpretations, which may over time lead different groups to use the same term (‘trust’) while meaning different things. Though patients consider trust important and link it to their perceptions of their health care quality (Barnes, 2013), I argue that divergent interpretations of ‘trust’ on the part of researchers,

clinicians, and potential research participants have contributed to the perceived 'crisis' of trust in biomedical research.

McKnight and Chervany give us a comprehensive model of trust constructs so we may begin examining different facets of trust—these comprise: Trusting Intention (*willingness* to trust even though bad things may happen), Trusting Behavior (*demonstrated* trust despite possible bad consequences), Trusting Beliefs (that someone is willing and able to act in one's best interest), System Trust (belief that an impersonal system has been constructed to enable success), and Dispositional Trust (trust based on life experience) (McKnight and Chervany 1996). We may use this as a starting place, recognizing that the literature is rife with attempts at adequately defining trust. (Gilson 2003; Colquitt, Scott, and LePine 2007; Hall et al. 2002). It is not truly the precision of the term I wish to contemplate here, however, but rather the *ways* in which different stakeholders within these biomedical spaces interpret the term.

Vocabularies of trust

When they speak of 'trust,' I argue, researchers and participants have different shades of meaning in mind. Potential participants appear to be using 'trust' as a term best understood when embedded in the language of patient-provider relationships (Kelley et al., work in progress). Trust for them is often primarily relational; providers who gain patient trust may more readily enroll patients in research studies or recommend different courses of treatment.

But for researchers and, increasingly, providers collaborating with researchers, trust is best understood contractually, represented by a set of actions meant to lead to further trust (King and Churchill 2008). Trust for them is intended more to lead to informed consent—trust becomes more shaped by function than by relationship, and by following formulas for building sufficient participant trust, they hope to conform to duties described by regulatory bodies and stave off

allegations of misconduct. Since researchers, regulatory bodies, and IRBs control informed consent as it currently functions in clinical spaces, they control ideas of how trust works and should or should not be cultivated within these spaces.

When we discuss how current informed consent relates to trust, then, we are looking through the regulatory lens and are discussing donors' rights as they pertain to scientists' needs (Boniolo, Di Fiore, and Pece 2012). The expansion of research and medical practice to large teams, Boniolo and colleagues argue, diffuses trust and renders informed consent nearly meaningless, since no one team member is well-informed enough to give all the information necessary for a motivated, informed decision to a donor (Boniolo, Di Fiore, and Pece 2012).

As the scope and scale of population-based medicine served by research increases, individual participants are being asked to trust increasingly diffuse entities who are more and more difficult to comprehensively name and whose aims could be more varied and diffuse as well. These participants must decide not only if they trust their providers in a relational sense, but if they should extend trust to organizations and systems of organizations as well.

Second, as the ethics meant to protect individuals are being shoe-horned into these larger and larger research collaborations, patients are being asked to consent to possible commercial involvements, which could further complicate the picture and might lead patients, for reasons of historic abuse and conflict of interest, to harbor greater hesitations about trusting this commercial involvement (Hoeyer 2013).

Rather than bemoan increasing complexity and commercial ties or add to the deficit-minded framing, however, let us turn to how trust already exists in research and health care settings.

Trust: It's already there

The biobanking literature is fertile ground for examining trust, and could be a proxy for trust in health learning systems as well. Studies have clearly shown both widespread ignorance about biobanks' purpose and function and simultaneous willingness to donate tissue specimens to biobanks (Simon et al., 2011). When surveyed, patients are almost universally willing to contribute tissue specimens to research endeavors (Steinsbekk et al. 2013; Goddard et al. 2009). Steinsbekk found that 69% of Kaiser Permanente members surveyed would be willing to give an extra vial of blood to a biobank, even though only 33% of those surveyed had ever heard of a biobank before. Respondents widely supported biobanking aims like diagnostic test development, targeted therapeutics and preventive medicine, once these aims were explained to them (Steinsbekk et al. 2013).

Learning more about biobanking goals actually increases patient willingness to donate, even when controversial research goals are involved (Lewis et al. 2013; Gornick, Ryan, and Kim 2014). Up to 85% of respondents surveyed in other studies expressed a similar willingness to contribute to biobanking, even after understanding they would not personally profit or receive personal results (Rahm et al. 2013; Kaufman et al. 2009; Goddard et al. 2009; Fitzpatrick et al. 2009). In populations actually asked to contribute specimens, up to 85% donate (Johnsson et al. 2010; Rahm et al. 2013).

Most of Steinbekk's respondents knew they would not receive a personal benefit in the form of returned results or financial payment; 74% of them were willing to contribute anyway because "it is important to contribute to research," and 56% had "no concerns about contributing to a biobank" (Steinsbekk et al. 2013). The trust participants vouchsafe their medical care providers predicts their willingness

to contribute to research (Steinsbekk 2011). Their trust levels in biobanks also predict their willingness to donate specimens—trust levels in this situation are more predictive than other factors like belief in health care benefits or education level (Critchley et al. 2012). Even populations with powerful incentives to distrust research and to decline research participation have been shown to be accepting of research under appropriate conditions (Buseh et al. 2013).

Given, then, participants' low levels of biobanking knowledge and awareness, their willingness to donate specimens, and the trust they already are placing in their medical care providers, we can see that trust is already present. It is merely located in a different place—trust is not being built between patients and biobanks, but rather between patients and providers and medical systems, as can be seen in development with the Mayo Clinic or with Kaiser Permanente, for example (Lemke et al. 2012). Trust in providers and medical systems could perhaps 'bleed over' to biobanking and health learning systems, then, with providers as its conduit. Biobanks and health learning systems could focus on how to properly channel this pre-existing, relationally-based trust instead of trying to forge their own versions of trust via consent forms and sets of procedures.

The 'crisis of trust' could then be more a matter of trust 'missing' where researchers are looking for it—between patients and biobanks, health learning systems, or other medical-research interfaces—than of trust being absent or withdrawn. The trust is not being placed in biobanks or health learning systems, I argue, because these projects do not have widely-known precedents, are still low in visibility, and do not display consistent regulatory practices. Sufficient trust already exists, however, to conduct successful research in clinical spaces, as long as the pre-existing trust relationships between patients and providers are invoked. Trust, in other words, does not need to be fabricated as much as it needs to be translated.

Furthermore, this existence of patient trust and the need for its translation, imply that biobanking and health learning systems ought to strive rigorously to recognize and preserve it while performing this translation. These systems risk losing valuable patient buy-in and informed consent if they fail to recognize the relational trust already vouchsafed in care team members by patients in clinical spaces—this represents a sobering opportunity for loss, not just an area ripe for translation, if it is not taken into account.

Trust is not (exclusively) contractual

Trust as it often invoked in biobanking literature is expected to perform functional tasks such as raising consent rates. For many projects, trust can be encapsulated by the mutual obligations set forth in the consent form—the form becomes the talismanic site of trust itself (Laurie and Postan 2013). Biobanking literature currently tends to place trust in this functional role, positing it almost as a figure in a mathematical equation: ‘If researchers and clinicians do x (actions to build trust), increased trust will then result in y (better outcomes for research, such as higher consent rates and a lower likelihood of scandal related to research misconduct.) The consent form, for both biobanks and health learning systems, is being viewed as a primary way to protect and document participants’ autonomy while also sealing trust between participants and researchers (Laurie and Postan 2013). But signed consent forms cannot stop there: they are also being asked to protect stakeholder interests and prove researcher integrity to overseeing IRB boards. This seems like a heavy collective burden for a few pieces of paper we already know patients do not actually read or comprehend well to bear (Anderson and Solomon 2013).

Laurie and Postan suggest that fetishizing the consent form and legalizing the consent process as the way to discharge all legal and ethical researcher duties to patients, and vice versa, could instead damage the researcher-participant

relationship while side-stepping effective ways to rely on trust instead (Laurie and Postan 2013). Biobank developers so far have recognized the importance of patient trust when obtaining specimens, but the conventional view still positions trust as a function of specific duties, much like Cadigan et al. put it:

For biobankers, the most valuable asset is the trust of their participants in their endeavors, a trust that requires the provision of all necessary information during the consent process and the existence of reasonable and adequate mechanisms to protect their privacy and the security of their data and samples. (Cadigan et al. 2013)

Trust, in this model, flows from information and data security. It does not capture the piece of trust that cannot be contractual, that rests on one individual's understanding of another unique individual and the kind of care that keeps the former individual from betraying the latter. At best, the consent form merely reflects a moment frozen in time. It permits no dynamism, none of the back-and-forth of either open conversation or the give-and-take nature of forming actual relationships (Laurie and Postan 2013). It is instead only a contract, one drawn up by researchers and approved by IRB members sympathetic to researchers or at least familiar with them—the form gives the signer no room for questions or for counter-negotiations. The consent form, then, is closer to a demand than a true contract, since participants lack true representation and have no way to alter the contract other than declining to sign. This is not a space of actual trust, then, but a space of created expectation. Trust has been whittled down to officious language on a printed page and has been drained of the flesh-and-blood dynamics that keep it alive within the patient-provider relationship. Instead, “consent ought to be reconceived as a continuing relational process. In these terms, the function of consent is to signal acceptance and trust in the research endeavor with all of its uncertainties and vicissitudes over time” (Laurie and Postan 2013).

Johnsson et al. also find this contractual portrayal of trust unsatisfactory and has written at length about the fiduciary and ethical duties to participants researchers must fulfill that cannot be discharged adequately by the consent form (Johnsson et al. 2013). As Johnsson states, “moral judgment must never be reduced to rule-following” (Johnsson 2013). The perils of expecting the consent form to adequately secure participant trust are myriad, not least of which, Johnsson et al. say, is the fact that truly informed consent can never be claimed, since broad consent, or even narrow consent, can never adequately describe exactly what research and methodology participants are agreeing to.

In any case, even if all pertinent information *could* ever be adequately conveyed, potential donors are still being asked to make the judgment calls on their own, uninformed by researcher expertise, by medical counsel, or by the chance to even hold discussions about it. As Johnsson summarizes:

Regardless of what consenting model one settles on, leaving risk-benefit assessment to donors is irresponsible unless one can reasonably assume that all donors will be well equipped to make them. The crucial question is thus not whether donors have a right to make such assessments, but rather whether the researchers have a duty to. (Johnsson 2013).

Researchers, *not* participants, are more fully equipped to judge risk and to likewise explain it. I agree with Johnsson that centering informed consent on consent forms instead of consent conversations absolves researchers and associated clinical staff from moral obligations. It also pares trust-building down to ‘proving’ transparency, accountability, and oversight. Were institutions able to do this perfectly, however, they would be *trustworthy*, but not necessarily trusted. They also will have succeeded in banishing the necessity of trust and will have converted trust into a legally-binding contract (Johnsson et al. 2013; Johnson 2013).

Trust as participants commonly understand it, however, cannot be contained by a contract. An institution's or research project's being trusted cannot be boiled down to discrete actions like providing more education, adding more layers of oversight, beefing up authority, or making promises (Jones and Barry 2011). This, from a participant's viewpoint, is likely an empty view of trust uninformed by the experiences and shared decisions that allow a patient to trust her doctor, and by extension, to trust a researcher wanting that patient's residual tissue specimen or her consent to randomization to standard care in a health learning system.

What looks like trust on participants' parts could instead be unconditional kindness or altruism, implying that patients are not necessarily trusting (Ashraf, Bohnet, and Piankov 2006). Behavior resembling trust could also mean participants assume a sound contractual relationship in which institutional regulation rather than personal accountability ensures their safety—this sort of trust comes not from informed choice but from an imbalance in power and knowledge and a resulting reliance on contracts written into law to ensure patient safety (Goebel et al. 2010; Goold 2013; Levitt 2011). The patient's evident trust could also be restlessness, anxiety, or an urge to hasten along a medical appointment, in which case the patient's apparently demonstrated trust is being exploited, or at least conflated by other pressing concerns in clinical consenting to research is being conducted.

Trust perspectives within relational ethics

Trust for patients could mean the acknowledgment that, within a working professional relationship with their care provider proven by time, they are willing to cede decisions about research participation to this provider, or at least to be confident this provider means them no personal harm and that they can then participate in recommended or associated research without much reason for concern. They are reasonably coupling the decision-making capacity they accord their care provider on the basis of greater expertise with their experiential

knowledge that this provider means them no harm (and in many cases has succeeded in demonstrating proactive care) and are extending these elements of trustworthiness to research spaces.

Trust when viewed from a researcher perspective, however, takes on a much more contractual appearance. Also reasonably, researchers are certainly not seeking to harm participants. They lack, however, the incentive to invest in personal patient wellbeing patients expect from care providers, and they possess additional incentives to protect themselves from allegations of ethical or legal abuse of subjects. Their attention, therefore, is not on forming relationships or on viewing trust as an extension of these relationships, but as seeing trust as the outcome of a set of systematic obligations laid out or at least hinted at in the consent document.

These are significant distinctions. I argue that these distinctions are bound to color the expectations participants and donors bring to the consent process and decision. If, as I have demonstrated, participants donate out of trust that primarily stems from their experiences and personal relationships with their care providers, then it is reasonable to assume that they may expect researchers to develop similar care-based relationships. Within these expectations, participants will expect researchers to recognize them as unique individuals and will want reassurances that their individual preferences and needs will still be respected.

Is this reasonable behavior for donors, or is this an example of the “misplaced” trust Johnsson believes should be corrected before actual trust can exist (Johnson 2013)? Do researchers have an ethical, if not legal, responsibility to correct this expectation and restore it to a trust based less on relational ethics and more on contractual ones (which would effectively, if it is done well enough, render trust useless as transactions will become so contractual it will erase the kind of risk we expect trust to bridge. Or should researchers realize what

expectations participants are holding and attempt to meet participants in this space? Researchers may wonder how to meaningfully demonstrate care for individuals—or for entire populations, for that matter—and this does seem puzzling. But it is also puzzling to think of asking participants to give over pieces of themselves for unspecified purposes at unspecified times without proof of good faith. In this case, as has been amply shown, consent forms fail to adequately demonstrate good faith, and merely appear to discharge a legal obligation instead, which does little to give participants the positive assurance they seek.

We can help navigate this question by examining what is at stake for a researcher versus a research participant. Who takes the greater risks and who holds more power or more likelihood of both experiencing greater benefit or less harm?

Participant versus researcher vulnerabilities

Morally and in the reality of the patient-physician space into which research is increasingly being woven, human tissues retain, at least in the minds of many of their donors, unique properties that entail levels of donor control, or at least of continuing obligation, beyond the act of donation (Master et al. 2013a). If tissues are discarded in the medical waste bin, this is a “waste” to be mourned from a research perspective, particularly in light of the potential many of these tissues have to advance important research frontiers. But at least the “transaction,” if we can even call it that, begins and ends cleanly inside the waste bin and no one has any expectations of the matter continuing any farther than incineration.

If, instead, the tissue is incorporated into a biorepository, the matter becomes more complicated than a waste bin, and more complicated than a consent form as well. The donation, I argue, strikes up a relationship, even if this appears completely one-sided or invisible from a researcher’s perspective. The

researcher has received the raw material needed to make progress in medically useful work, a kind of work run much more along industrial lines than donors perhaps realize, and an environment in which a single specimen hardly ever makes more than the briefest ripple of an impact. The researcher is concerned with numbers and uniformity, and, due to his or her understanding of research requirements, norms, and rigors, is not likely to regard this specimen as anything more than a label and a data-point—for the researcher, it is the sum and the measurable uniformity of specimens that matter, and rightly so, since they are in search of emergent, medically meaningful patterns and correlations. The idea of holding any kind of continuing obligation, or of entering into some kind of “relationship” might seem both slightly ludicrous and certainly logistically impossible from this perspective.

Pivoting around to the donor perspective, however, we see how it is logical to hold expectations that the recipient will not do anything shameful or offensive with the entrusted specimen—we see how a donor could be both willing to give residual specimens and solicitous on their behalf. From this perspective—empathizing with the viewpoint many donors take, of their tissues being special and still being, to a point, under their control—one sees the sense in donors desiring regular updates, tailored information if applicable, and the possibility of having a hand in deciding which specimens will be used for what or of having the opportunity to reconsider research the participant might reasonably consider offensive (Gornick, Ryan, and Kim 2014).

The difference between these positions rests on the stakes at hand for each. An individual specimen, to a researcher, is quite low stakes and is expected to merely add a few grains of knowledge to a dataset. The stakes run much higher for the donor, who sees the donation as a continuation of self—as cells containing the chemical (and perhaps ephemeral) essence of self, and possibly as a link to future news on either an individual or group basis. The specimen, in other words, is special to the donor, both by reason of its essence and by

implication. Donation as an act—at least as many donors perceive it—could result in beneficial contributions to larger populations, in information that might indicate certain medical actions, or at least in an interesting update about research outcomes. Donation is more loaded, then, and this is a case in which *both* perspectives are not irrational, and we can see how it is reasonable for patients to believe they should retain some degree of control over deciding what happens to their specimens (Master et al. 2013b).

We must acknowledge that specimens are special to researchers and donors, but in different ways, and these different ways entail different expectations and duties. People are unique, seek to be “seen” as unique, and as not lost in the shuffle. Helpfully, this aligns with the medical mission of providing personalized care. However, if we can aim for personalized care, why not aim for personalized consent as well?

Trust as living in relational ethics: ethical obligations of trust

Physicians already have heavy responsibilities toward patients, both medically and relationally (Holwerda et al. 2013). Betraying a patient’s trust in a treatment environment can injure patient health outcomes—and if physicians must also represent researchers and maintain patient trust in research within health learning systems, they arguable bear an even heavier and more complicated burden within the framework of relational ethics. How are they to discharge these responsibilities? And must they bear *all* this burden?

Along with Johnsson, I argue that researchers bear responsibilities toward patients and participants that run deeper than the consent form and that cannot be contained by regulatory approaches (Johnson 2013). Much as regulations attempt to ensure ethical behavior toward participants on the behalf of researchers, they do not require researchers to maintain personal relationships with participants. Care relationships that stay personal for patients and

physicians are *not* personal for researchers—an imbalance of care has then been introduced along with an imbalance in the kind of ethical duties implied by a personal relationship. Participants, then, must extrapolate what it means to be in relationship with a researcher. This process of imagination could lead to discrepancies in what the consent form promises and what the participants hopes for or expects. As Johnsson puts it: “When cast in the role of the peg, donors must navigate a novel situation shaped by academics’ views on what it means to be informed, while attempting to find meaning along the way.” (Johnson 2013).

Recognizing that participants have expectations that may not necessarily align with what researchers can offer, researchers have a moral obligation to consider these expectations and to consider partnering with care providers in developing meaningful relationships. Researchers need a new model, one based not on convenience and on relying on clinics to accomplish the consenting part of the work, but one based on relational ethics and on consistent procedures that are created ground-up to conform to what works for all parties involved instead of being uncomfortably wedged into pre-existing clinical procedures.

Not only does cultivating personal relationships with patients promote patient and population benefits, it avoids doing the particular kind of harm that comes from conducting research while remaining blind to the needs and interests of the groups being researched, as with the Havasupai, or by refusing to establish the kinds of relationships and understandings that could check a researcher from conducting ‘helicopter research’ or otherwise disregarding community desires for relationship over research done at a remove. Buseh et al. quote a participant from a minority community while reminding researchers that care matters:

Anybody who wants to do research on us needs to be in the community before you come talking about doing research. We have to see you regularly to believe that we can trust you to advocate for our issues. We have to know you, know that you are good people. We have to know that you will not misrepresent us. (Buseh et al. 2013)

Buseh et al. include another participant quotation that vividly illustrates the importance of care-based relationships in preventing historic harm and the continuing harms of underrepresentation:

We have to be treated with decency and respect. As a race of people we have been demeaned for hundreds of years. We need to be acknowledged for what we give to the world by being in research. In Henrietta Lacks we see somebody who gave something to the world and was never acknowledged. As African Americans, our attitude toward the healthcare system and medical research in general, is still sullied by the reverberations of racism and the discrimination that continues today. Unless there are fundamental relationships built, there will be no successful genetic projects. (Buseh et al. 2013)

Though the means of developing these personal relationships may present some difficulties, researchers recognize the importance of personal narratives that can shed light on consent and research proceedings. Researchers have been willing to join patient engagement efforts by participating in community conversations and by implementing community advisory boards (James 2014, work in progress). Nor do researchers need to stop there. I argue researchers could do more to publicly demonstrate care at the population-based level, such as sponsoring academic scholarships for future researchers from particular communities or by themselves taking a hand in patient consenting. Increasing their community visibility gives researchers a powerful opportunity to demonstrate the elements patients have identified as the important components of successful physician-patient relationships: transparency and genuine care. To support shared decision making and the strong relational ties that can lead to trust, researchers can a) invest from the beginning, b) be attentive to patient perspectives, c) show active empathy, and 4) invest at the end (Matthias, Salyers, and Frankel 2013). These are simply solid relational principles, but if followed could increase the success of related research as well.

Genuinely building trust can be accomplished as long as a repository a) shares its power and responsibility, and b) finds advocates with “safe hands” and

overseers who understand the community's interests (Levitt and Weldon 2005a). Earning trust means instituting a deliberate plan, demonstrating reliability, and making a series of (perhaps small-seeming) decisions to intentionally craft relationships, one day at a time, with a backup plan for when trust is damaged.

Trust-building need not rest exclusively with physicians or researchers—other members of the care team, or staff appointed specifically to form relationships within consenting protocols can assist as well (Yamada et al. 2013)

Obtaining informed consent from patients is a time-consuming process (our 10-page Informed Consent Form takes approximately 45 minutes to review with each patient and their family) that is best done by highly trained nurse coordinators who meet regularly with the physicians involved in surgical decision making. It is also best done by nurses with whom the patients are familiar (e.g., from outpatient clinic visits) and have developed a relationship of trust. (Yamada et al. 2013)

Participants can also be invited more deeply into research decisions. The paradigm of citizen science within biobanking and health learning systems could be an appealing way to enter new collaborations and relationships (Meir et al. 2014).

Of course, we're leaving out an additional, increasingly vital perspective: that of the physician and staff expected to secure and administer consents. This facet of modern consenting sets stakeholders up for disappointment, I argue, even if all parties approach the interaction with goodwill. The researcher wants ethically sourced, uniformly collected and thoroughly annotated specimens; the physician wants as little intrusion upon clinical time as possible and as streamlined a process as can be managed; patients solicited as donors want excellent care (first) as well as time to consider the actions being requested, chances to ask questions about these solicitations, and chances to survey what kind of relationship might issue from this interaction.

These goals do not neatly align. Which is not to claim that there is no solution, or that we must not rest until we find a solution equally tenable to all. Still, we must

keep the overall picture as well as the individual stakeholder perspectives in mind as we juggle possible options to address this clearly loaded consenting environment.

Solutions

One possible solution is for researchers to treat specimen procurement as an economic transaction and to purchase specimens through treatment centers, hospitals, or independent sourcers, since this may bring more transparent regulation to a process formerly dependent on donations. Clearly this option piles costs onto already expensive research studies and could present its own tangle of ethical questions along with the costs. However, costs could be kept down by performing actions in bulk, and the transaction in this sense could be very clearly defined so that only those comfortable with releasing their specimens regardless of future implications sell their specimens. This solution could introduce potential bias in terms of who is willing to sell their specimens (while also introducing greater consistency in annotation and collection/storage methods). Price point is also an objection: too low, and specimen-owners will not wish to sell or go through the inconvenience of collection. Too high, and research progress is hobbled even more than it already is. This solution solves some of the ambiguous obligations and expectations involved, but at a considerable cost and, I judge, is unlikely to appeal to many.

This solution also highlights a current discomfort in clinically-related consent: donors are expected to give specimens or participate for free without clearly defined payback. This parallels expectations in blood and organ donation, though I argue that it differs in that, with the former, an individual donates with the expectation he or she is directly benefiting another individual. This preserves individual ties, even if the beneficiary is a stranger, and also, due to this “localization”, limits the potential harms while strengthening the altruistic “reward” donors often feel for their selflessness. Donating to biobanks or participating in research within health learning systems diffuses these person-to-person ties and

spreads both altruism and benefit widely across potentially huge populations. The donation risks are also spread more broadly, depending on the donor's perspective. After all, the donor is not being asked to donate a few pints of blood to a single medical team infusing a single patient—they are being asked to release personal tissues to multiple unknown entities for multiple unknown purposes broadly described as 'research.' The literature shows that people are still largely willing to donate under these circumstances (Gornick, Ryan, and Kim 2014), but I argue for ethical purposes that they may still be donating "in the spirit" of giving blood or an organ without the situation being similar enough to warrant this attitude. Depending on the donor, the risks may seem minimal, and it may even feel better to spread one's potential assistance across a wider swath of the populace—on the other hand, the spirit of giving to a recognizable entity has been diluted, and it may not be fair to expect donors to give "without strings" when the actual conditions of biological donation have been shifted so much.

In other words, blood donation is often used as a comparison, but one which could obscure certain factors donors may wish to more deeply consider while appearing to absolve researchers of duties donors may implicitly expect. Why is it unreasonable, after all, to take umbrage at some donors' frustration about not being recompensed for their contributions, when money is changing hands at every other step of the way in the research pathway, and when (at least from some donors' perspective), some researchers and companies stand to gain a great deal, professionally and monetarily, from research based upon these specimens? Perhaps it is reasonable to consider alternate payment structures, or to take seriously ways of recognizing donor participation without continuing to take donations for granted.

At the moment, researchers do not *need* to recognize donor contributions, and do not officially even need to use consent forms to collect residual tissues. As medicine and research rely upon larger and larger datasets that incorporate more personal annotated information, it is becoming increasingly naïve, however, to

cling to the idea that these specimens can continue being sourced for free without informing donors and without strings.

Positive ethical opportunities

Researchers can go farther—an opportunity is here to push beyond “minimum obligation” levels that simply shield researchers from lawsuits and recrimination while checking a variety of boilerplate boxes to a place where researchers and donors can either truly collaborate or can at least hold open conversations about the work going on with an eye toward including beneficence and the desire to respect patient wishes.

As the NIH highlights, injunctions to foster public trust without proper governmental, institutional, and financial support ring hollow. Scientists and clinicians must also shift their own culture to place a premium on demonstrated, transparent trustworthiness occurring not just once, but over a sustained period of time, that actually consults members of the public and remains open to their ideas in recognition of the biovalue they create (Mitchell 2010). Authentic partnerships with established community organizations are encouraged, as is communication that continues after the initial donation. Ongoing communication demonstrates respect for participants’ original contributions, builds trust by consciously maintaining transparency, and helps fulfill known patient wishes, such as some patients’ acknowledged desire to demonstrate altruism (Forsberg, Hansson, and Eriksson 2009). In fact, to whatever extent is possible, the NIH recommends that institutions forge bi-directional relationships with their patients to both a) demonstrate respect and clarity and to b) solicit valuable patient feedback while enabling opportunities for mutual education (NIH).

Cultural Context

We must not forget the importance of cultural context in general. Motivations for participating will sometimes differ importantly by race (Shaz et al. 2009), so it makes little sense to treat a pool of potential participants uniformly. Though many

participants are likely to be middle-aged, have children, identify with a positive outlook on medical research, have previous disease experience, and report a positive track record with medical institutions and clinicians (Fitzpatrick et al. 2009; Sanner and Frazier 2007), these are not the only potential participants.

Tailoring communication, outreach, and trust-building efforts to specific populations may be time-consuming and challenging, but the costs of refusing to tailor simply continue to promote flawed ways of communicating and gaining trust. Instituting clearly-defined laws and legislative oversight on biomedicine conducted with minority volunteers may provide one means to reassure donors and increase trust (Ma et al. 2012).

Institutions have easily accepted tissue specimens or consent to enroll patients in research, including research on medical practices, as gifts from patients (or even as rights) but patients may be giving these gifts not so much as presents to science as out of desire to receive the best medical care possible (Levitt and Weldon 2005b). The gift relationship frays particularly when donors suspect that a biocollection may be conducting research both with funds from public taxation and with funds derived from specimen sales to private firms and pharmaceutical companies (Fitzpatrick et al. 2009). This blurred purposing of specimens likewise blurs the gift relationship and erodes trust (Glaser and Bero 2005; Haddow et al. 2008; Levitt 2011). As one UK participant commented: “I think it’s a moral question as well. We’re not talking about a Dyson Hoover here, we’re talking about people’s health and well-being here and I don’t like to see it patented.” (Levitt and Weldon 2005b). Simply disclosing commercial ties does not “cut it,” either—even after disclosure, conflicts of interest could tempt researchers to (perhaps unconsciously) subsume public interests in favor of profits (Glaser and Bero 2005).

Building trust can be done, though, according to community consultations, as long as a biocollection a) shares its power and responsibility, and b) finds

advocates with “safe hands” and overseers who understand the community’s interests (Levitt and Weldon 2005b). Participants do not want to be the only ones in charge of providing information along with their specimens—they would prefer the informational obligation to go both ways. Rather than asking participants to simply trust a biocollection’s purposes no matter what, some researchers point to how “trust will be restored only if the public have ways of judging matters for themselves” (Levitt and Weldon 2005b). Previous gift-based models like organ donation and blood banks differ from biocollections because organ donation and blood bank participants can safely assume they are giving directly to ill people who will directly benefit from their gifts. But with a biocollection participants cannot be sure their efforts directly support sick people, meaning it may be more appropriate to portray their trust as “an emergent property of good social relationships that are built up over time” with a biocollection institution rather than as a discrete, no-strings-attached gift (Levitt and Weldon 2005b).

Interpersonal interactions are also crucial. Even one personal relationship with a researcher can influence participants’ trust and understanding of biomedical goals (Gilson 2003). While the individual researcher may be charismatic, particularly communicative, or successful at public presentations, however, the individual cannot, and should not, be completely separated from the matrix of his or her host organization. Individuals may mediate an organization’s relationship with members of the public but cannot account for all an organization’s decisions, particularly decisions that generally go unaddressed, like how biocollections handle data linkages between specimens and participants’ medical records (Miller) So building trust should incorporate opportunities for individuals to interact and for institutions to demonstrate commitment to transparency. Public trust can “bleed” from clinicians to researchers and vice versa, making it vital for clinicians to place a priority on positive clinical encounters with patients and for researchers to make outreach efforts and to avoid breakages in trust, especially since patients have likely already had challenging interactions with clinicians (Rothstein 2010; Gilson 2003).

Nurturing public trust will also pay off by helping health organizations avoid the litigation, negative campaigns and other fallout that results from building bad relationships with patients and media representatives. Clearly, building trust is not necessarily an easy, affordable, or clearly marked path, but it pays to “Hold onto the virtue” (Paine 2007). Be upfront, Paine advises, about conditions as they really are, demonstrate personal and organizational character, and do not “spin” conditions (Paine 2007). Building trust, essentially, is performing the tough, important, rewarding work of building individual relationships that lead to overall institutional integrity (Gilson 2003; Schee, Groenewegen, and Friele 2006). Earning trust means instituting a deliberate plan, demonstrating reliability, and making a series of (perhaps small-seeming) decisions to intentionally craft relationships, one day at a time, with a backup plan for when trust is damaged.

This type of instrument is a jumping-off point, though other dimensions of trust can also be measured, keeping in mind: a) how “public” trust should be measured inside as well as outside of an organization, b) how ‘trust’ is often influenced by specific cultural interpretations, c) how communication behaviors influence trust, d) how trust can be dynamic over time, and that taking a single point of measurement does not capture this dynamism, and e) how trust has cognitive, emotional, biological and behavioral elements, all of which should be considered in a comprehensive model (Gilson 2003; Paine 2007). Personal relationships are not everything, of course, and must be balanced, as Levitt reminds us:

Closer relationships would incur more costs that have to be balanced against the benefits where the aim is to maximise the use of the resource by researchers and ultimately to improve health care for the whole population. (Levitt 2011)

These considerations give us a broad range of data points to potentially collect and evaluate as part of the trust-measuring process.

We should also remember that patients are likely to trust clinicians due to society's expectations that the clinician will be impartial and well-meaning (Gibson 2007). However, the patient is trusting in the face of significant inequality in terms of medical knowledge and power, meaning what looks like trust might actually be dependency lacking a true choice to trust—this is why ethical codes attempt to mandate trust-worthy behavior (Gilson 2003). This contractual sort of trust can eventually morph into a more empathic trust based on emotional bonds and cognitive recognition of the clinician's (and, by extension, the researcher's) interest in the participant's wellbeing over time (Gilson 2003). Biocollections should foster personally-grounded relationships between clinicians and participants and between researchers and participants if they truly want to claim they have invested in public trust. These relationships should acknowledge that trust comes easier for those in privileged positions and is harder to establish with those less privileged. So when building trust, it becomes particularly important to promote chances when citizens, healthcare professionals, and researchers can personally meet and can begin to personally understand one another's viewpoints while practicing mutual decision-making—these interactions build actual trust while setting up the appropriate structures to maintain it. Organizations may offer reasons to trust them in their rules and mission statements, but without personal accountability these statements remain merely glib (Gilson 2003).

Trust is one of the primary factors feeding into a patient's consenting decision, and has linked positively to participants' intentions to participate in biomedical research; trust in medical and scientific authorities plays a much more substantive role in patient decisions than does patient beliefs about benefits or comfort (Critchley et al. 2012). In biobanking, trust in researchers correlates positively with participants' willingness to contribute to biobanking research (Javitt 2013). But despite the established importance of trust metrics and of building potential donor trust within the spheres of biobanking and health learning

environments, trust remains underemphasized within current regulatory frameworks (Javitt 2013).

As explained by those interviewed, patient trust is built through a number of factors, including internal, inherent factors (such as the assumption that medical facilities are upheld to ethical standards of conduct) and the assumption of care within biomedical settings, and external factors such as the communication of transparently ethical practices, the establishment of acceptable oversight, and the ongoing process of communication research results.

Researchers can strengthen the trust patients already bring to the medical field by issuing regular updates, by including information about oversight, and by carefully recruiting minority patients in culturally appropriate ways—these means of trust-building convert trust from a somewhat ambiguous or taken-or-granted set of actions to discrete protocols that convert assumed trust to demonstrably informed trust (Beskow et al. 2010; A. A. Lemke et al. 2010). Scientists and clinicians must also shift their own culture to place a premium on demonstrated, transparent trustworthiness occurring not just once, but over a sustained period of time (Mitchell 2010).

Trust is also built by fulfilling signed or assumed contracts between patients and researchers. Though donors may understand the limitations of the consent form they sign, they still, when explicitly asked, expect researchers to fulfill reciprocal obligations (Murphy et al. 2009). Oversight and penalties for abuses helps build trust (A. A. Lemke et al. 2010), as does reputable associations with non-commercial entities (Korts, Weldon, and Gudmundsdottir 2004). Behavior resembling trust could also mean participants assume a sound contractual relationship in which institutional regulation rather than personal accountability ensures their safety—this sort of trust comes not from informed choice but from an imbalance in power and knowledge and a resulting reliance on contracts written into law to ensure patient safety (Goold 2013; Levitt and Weldon 2005b).

Trust slips into mistrust when donors' needs and expectations are ignored. Opportunities for mistrust to flourish include spaces in which potential participants lack sufficient scientific information, when reliable oversight is lacking, when conflicts of interest and/or profit-making exist, and when regulations are made to suit institutions without acknowledging public needs (Levitt and Weldon 2005b). These spaces of mistrust were mentioned by the participants I interviewed as well—participants expressed greater suspicion about ties with commercial entities and about insufficient levels of information. Racial minorities, who have much to lose from breaches in trust, have also expressed mistrust of research aims, particularly without proper accommodation (Duster 2006; Bussey-Jones et al. 2009).

Conclusion

Patients' and participants' trust, in both individuals and institutions, as well as in the biomedical sciences themselves, is a foundational concept for the success of biomedical research. Interpersonal relationships help shape trust, and the relationship between the arena of research conducted with patients, and important lessons can be learned from examining how trust applies to patient-provider relationships being expanded to patient-researcher relationships.

Chapter 4: When to waive: Waivers of documentation of consent in health learning systems

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Introduction

Patients and the public stand to benefit greatly from research on medical practices (RoMP) within health learning systems that systematically compare standard medical treatments to determine which treatments result in the best patient outcomes (Kim and Miller 2014). RoMP, however, raises complicated ethical and regulatory questions (N. Kass and Faden 2013), not least of which concern participant consent practices.

The actions taken by the Office for Human Research Protections (OHRP) in the wake of the SUPPORT study, coupled with mounting ongoing debate and commentary, hint at the degrees of regulatory uncertainty with which participant consent to RoMP has been viewed (Macklin, Shepherd, and Einstein 2013; Magnus 2013; Wilfond 2013). The relatively novel convergence of research and treatment goals within RoMP presents unique considerations, including the analysis of risk, the function of the patient-provider relationship, and “the ethical obligation to give prospective subjects sufficient information to make a knowledgeable decision about whether or not to participate” (OHRP 2014).

As has been expressed in the most recently released OHRP recommendations, (which are still awaiting public comment), participants are to be informed of all “reasonably foreseeable risks of research,” including risks related to standard of care treatments participants would not have received outside of research. The method of informing participants and of obtaining consent must comply with current Common Law rulings—fully informed consent must be obtained and may not be waived, though space exists in which to decide the details of consent procedures within health learning systems.

While the regulatory landscape is still relatively malleable, it behooves us to explore how the existing regulatory mechanisms governing consent can guide the fulfillment of OHRP recommendations while also seeking fulfill the spirit as

well as the letter of the law. Within this regulatory landscape, for example, we can take actions to promote strong patient-physician relationships, to smooth the juncture between research and clinical practice, to provide relevant information to patients making decisions, and to ethically respect patient preferences.

One way of doing so is to permit a waiver of documentation of consent whenever possible.

Consent practices in health learning systems

As standard of care cost effectiveness research (CER) develops, the regulatory climate is attempting to develop along with it to accommodate unimpeded clinical practice without leaving patients exposed to higher-than-minimal risks. Debate over acceptable definitions of consent for these CER activities has driven the proposal of a wide range of consent options. While a number of proposals have developed alternatives that would alter or waive standard informed consent requirements altogether (Faden et al. 2013; Kim and Miller 2014; Wendler 2013), critics remain reluctant to shift standard informed consent norms due to concern about abandoning fundamental aspects of human research protection (Macklin, Shepherd, and Einstein 2013). OHRP sides with this latter position in classifying standard of care CER as research subject to Common Rule regulations, including the disclosure of clinical risks of the treatments being compared, since these are now to be included as reasonably foreseeable research risks:

If evaluating a particular risk of research associated with a standard of care is a purpose of the research, then in general OHRP considers that particular risk to be “reasonably foreseeable.” Such reasonably foreseeable risks must be disclosed as risks in the informed consent process in accordance with the regulatory requirements of 45 CFR 46.116(a)(2) (OHRP 2014).

These reasonably foreseeable risks may be disclosed under 45 CFR 46 during a traditional consent process involving giving participants handouts detailing the possible risks and benefits of participating in the research as well as obtaining participants' signatures on a consent form.

However, allowing a waiver of documentation of consent instead of using consent forms with signatures, particularly when the standard of care treatments being considered are in equipoise, could strengthen the consent process and the respectful disclosure of foreseeable risks.

Waiver of documentation of consent

Under current Common Rule regulations, documentation of consent may be waived for confidentiality concerns or if the research “presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context” (§46.117.2(c)(2)).

Given the relative newness of RoMP within health learning systems, no consensus about how to view potential RoMP risks and benefits has yet arisen—significant ongoing debate surrounds the question of whether RoMP presents more than minimal risk, for example. (Macklin et al., 2013, Faden, Kass, & Whicher, 2013). Adding to the complexity, patients may perceive risks differently than do clinicians or researchers, and these views should be kept in mind when assessing risks and benefits as well (Sabin et al. 2008).

OHRP holds that “The risks of research in a study include those risks of therapies that some participating subjects would face that are or could be different from the risks of therapies they would have faced without participating in the research study.” Studies whose aims include comparing the outcomes of different treatment risks are by nature comparing treatments whose risks are not known at the outset, and the this possibility of differing risk, OHRP holds,

necessitates disclosing any identified risks particular to these treatments to participants as part of informed consent if the risks are more than minimal.

Researchers appear to need to determine under these circumstances if the risks related to treatments being compared are more than minimal, and if they are more than minimal due to their clinical nature or to them being risks of RoMP. Standard of care CER is designed to compare standard treatments whose relative risks and benefits are currently unknown, making prospective assessments of comparative risks and benefits very challenging. It will likewise be challenging to determine what treatments a participant may or would have gotten outside of RoMP activities being conducted, since RoMP studies are designed to compare treatments patients may or would reasonably be assigned during standard clinical practice.

Whether in standard practice or in RoMP, not all treatment risks are more than minimal. In RoMP where foreseeable risks to participants are no more than minimal, or where the treatments being compared could reasonably be in equipoise, a waiver of documentation of consent is advisable because of the likelihood it will increase patient understanding of risk and could strengthen clinical patient-provider interactions concerning disclosure of information and of consent.

Signed consent forms vs. waiver of documentation of consent

Documentation of consent using signed consent forms does have a few advantages. Since this process requires the patient to make a clear decision, a signed consent form could have symbolic value as a mark of respect. The signature allows the patient to openly record their personal choice, and could have a psychologically positive effect as a function of attaining decisional closure.

Documentation of consent can also appeal to professionals by offering a very robust level of proof of participant consent to guard against allegations of

institutional misconduct (Janvier 2013).

Within RoMP, though, consent procedures that depend upon a participant's written signature may weaken consent by assuming the information given to patients in this context has been adequately read, absorbed, and considered in ways that fulfill fully informed consent. When using signed consent documents that detail the risks of all treatments a patient may receive in RoMP activities, a patient's need for complete information could be unfortunately pitted against that patient's equally important need to comprehend the information being conveyed (May, Craig, & Spellecy 2007). As Wendler sees it, the current practice prevalent in some cases of disclosure of listing both practice-related and research-related risks in consent documents obscures clarity, buries the actually relevant risks that are distinct from standard of care-related risks, and heightens the perception of risk entailed in consent (Wendler 2013).

Additionally, Anderson reminds us that even immaculately crafted, thorough consent forms can cause confusion or at least fail to improve patient understanding (Anderson and Solomon 2013). Furthermore, humans, particularly humans under the pressures of limited time and unlimited stress, are not, as Rees reminds us, "information-processing risk assessors" (Rees and Gainty 2013).

Since RoMP approaches are not yet widely known, it would be naïve to assume patients will readily understand them, particularly when they are described in forms patients have little time to read or consider, and this lack of comprehension could hamper patient understanding, which would compromise the standards of informed consent (Carmen and Joffe 2005) and could also risk structuring consent to RoMP as a one-time decision instead of an ongoing process of freely-chosen participation (Wendler 2013).

Relying on consent forms with signatures could also result in damage to the patient-provider relationship if patients feel inadequately informed or unprepared

to unpack the risks presented in forms and handouts by themselves. This is not to claim the form is unnecessary—with waiver of documentation of consent, patients could still be given informational handouts—but shifts the responsibility of ensuring the patient understands the risks present and has had a chance to clarify them via personal—not merely legalistic—interactions.

The act of signing can also imply higher levels of patient responsibility and can feel “binding” in a way that highlights patient responsibilities and conveys a sense of contractual inflexibility not conveyed by the informality and relational care providers can demonstrate during verbal consent. Additionally, a lengthy consent document administered without adequate clinical support and chances to engage in bidirectional dialogue could exaggerate the implications of the decision (Meadow 2013).

Finally, documentation of consent may not fit the needs and expectations of minority communities who might be unaccustomed to the norms of consent or who may emphasize oral decision-making over consent as indicated by signatures (Carmen and Joffe 2005).

As the influence of RoMP and health learning systems increases, it would be logical to begin normalizing the practice of research being conducted within clinical spaces. Waiving documentation of consent could aid this normalization by lowering the barriers between traditional norms of research and clinical care. Documentation of consent, on the other hand, will likely keep these barriers artificially rigid.

A waiver of documentation of consent may relieve some of the tensions mentioned above by making patient-provider conversations more likely. Once documentation of consent is waived, clinicians or consent specialists could be under greater pressure to ensure consent through bilateral conversations. We argue that these patient-provider conversations can better align with patient

needs and preferences by presenting risk-related information in a manner more likely to ensure patient comprehension and choice.

Verbal consent for medical treatments combined with charted notes is standard of practice in many clinical cases, and the procedures being compared in RoMP, assuming clinical equipoise, are similar to these cases. Kim and Miller make the point that signed documentation of consent may skew results within health learning systems since it signals participants that something unusual is happening with the treatments they are being given. Since the treatments being compared are already standard practice and the level of uncertainty inherent in clinical decisions made by individual providers could be perceived as roughly equivalent to the level of uncertainty due to randomization being used as a research technique; these authors argue that signed consent forms would be inappropriate (Kim and Miller 2014).

Documentation of consent could still be acceptable if we could be sure that patients are indeed fully informed and that the patient-provider relationship is being respected and preserved, but, based on current clinical practice concerning consent and the literature surrounding it, we believe that permitting a waiver of documentation of consent is more liable to result in the fully informed consent and ethical respect advocated by OHRP.

Waiving documentation of consent has met with success in-person consent conversations coupled with notes made in patients' charts, for example, can achieve better outcomes than do formally signed consent documents (Sulmasy, et al. 1994).

Discussion

Upon considering the advantages and disadvantages of documentation of consent, as outlined above, it becomes clear why Janvier, acting as a parent, would not want documentation of consent, but, acting as a clinician, would opt for

it (Janvier 2013). Patients' interests may find themselves opposing, or at least straining against, institutional interests. Balancing patient needs of being fully informed against institutions' understandable desires to provide as much legal and ethical protection for themselves and their clients as possible becomes a delicate juggling act, and the appeal of tailored intermediate models increases.

Patient consent conversations, already a norm within clinical practice, seem a natural place to situate similar conversations regarding the risks and benefits inherent in the kind of research being conducted within health learning systems.

The farther one moves from the formality of the admissions desk, and the closer one moves to the relational trust being developed within patient-provider interactions, the more likely it seems truly informed consent is primed to take place. We recognize, of course, that consent indicated by a signature may be ideal in some clinical settings, or that expecting complete consent procedures to practically fit into already cramped physicians' appointments could be highly unrealistic (Capron 2013), but we also point to exemplar cases in which waivers of documentation of consent to randomization between standard of care have already found success (Myers, et al, 2014; Sulmasy, et al. 1994).

Documentation of consent using signed forms does not, of course, preclude personal consenting conversations that also facilitate patient autonomy, promote strong care-based patient-provider relationships, and meet the definition of informed consent. However, reliance on a signature as the ultimate sign of consent may downplay the primacy these kinds of conversations should be given and could lead to more weakly informed decisions. Without emphasis on personal interactions devoted to discussing consent in a bi-directional manner, patients may be more likely to read forms in a more cursory manner and may be participating in a more weakly informed decision-making process.

Furthermore, the signature line implies a firm contract without giving a patient the capability to clarify or negotiate what they are signing—though a patient could conceivably both have a personal consenting conversation with her or her provider *and* sign a consent form, the lack of a signature line and the necessity of noting consent-based conversations in patient charts could lead to better consent conversations, to higher degrees of informed decision-making on patients' behalf, and to lower levels of regret.

One main advantage of documentation of consent is the degree of legal protection it affords. Though signed consent forms may be more appealing to institutions in terms of proving legal consent, this level of legal protection can be duplicated by recording consent conversations in clinical environments, however, if it is done carefully enough. Patient notes shielded researchers at the Fred Hutchinson Cancer Research Center (FHCR), for example, when patients sued the center for improper consent procedures. FHCR was able to prove consent by producing careful documentation of verbal consent providers had made in patient notes (Lin 2004).

Legal reasons alone should not prevail, however—even if documentation of consent meets regulatory requirements, it may not adequately support ethical concerns guiding consent in the first place. As mentioned above, expecting a consent form administered without an accompanying personal conversation to cover all applicable ethical bases risks harming patients through inadequately explaining the possible repercussions of research—more abstractly but no less impactfully, harm could also be caused by foregoing an opportunity to cement a healthy patient-provider relationship within the health learning system by discussing how participation in the system could benefit (or harm) a patient on both the personal and population-based level. This clinically-oriented conversation preserves the transparency and shared decision-making possible in patient-physician interactions, and could both honor patient expectations and the clinical normalization of health learning systems (Meadow 2013).

A waiver of documentation of consent may permit greater levels of autonomy, and may help a patient feel respected more within the decision-making space, since verbal consent protocols give patients more chance of personally airing their concerns and of processing the decision with a professional more familiar with the decision's implication than the patient likely will be. We acknowledge that a clinician may not always have time or, frankly, the inclination to conduct consent conversations in already demanding clinical environments. This is a logistical hurdle, however, and could be amended by altering clinical spaces and workflows to better fit stakeholder needs as health learning systems develop.

In some ways, providers, due the unique trust patients place in them, are key to the success of informed consent within RoMP. Consent can be mediated by patients' trust in their providers—patients trust the providers will advise them to participate in research opportunities that have the potential to benefit them or people they care about; patients also trust their providers will be adequately transparent about research risks and rewards. The patient-provider relationship, then, stands in as a proxy for a longer and more laborious consent process—it is a “shorthand” way to reach consent, not sloppily or with intent to simply make everything as expedited as possible for researchers, but as a means to communicate with patients in a way patients judge both thoughtful and adequate (Mazor et al. 2009).

Conclusion

Comparing an informational form against the identical form adding a signature line, we notice how the consent signature fulfills a variety of primarily contractual functions. We contrast this with the number of relational functions fulfilled by shifting the signature off the consent form and “into” the consent conversation. As health learning systems progress, they will need to determine which functions hold more weight, and will need to advocate for policy revisions accordingly. We

recommend including a waiver of documentation of consent among these revisions.

Particularly when treatments being compared within RoMP activities are in equipoise as far as can be known, permitting a waiver of documentation of informed consent allows for a strong consent process while simultaneously side-stepping some of the obstacles presented by standard documentation of consent.

DISSERTATION CONCLUSION

As technology expands our capacity to design ever larger and more complex studies and to collect and analyze larger and larger patient data sets, we should not lose sight of the role personal relationships and trust play within clinical environments.

As I hope I have demonstrated in the preceding chapters, technology enables capacity and can lead to more insightful research results, but the trust that convinces patients to let researchers collect and analyze their tissues and data is fed by caring relationships, not by greater data sophistication or by more finely tuned consent forms.

To quote a chestnut, 'Actions speak louder than words.' The empathy and demonstrated interest in a patient's wellbeing a provider evinces appears to mean more to a patient than any number of consent forms and contractual promises. This is not, of course, to suggest dispensing with consent forms and careful adherence to regulations protecting patient interests, but it is to pointedly emphasize the dominance and influence exerted by the patient-provider relationship.

Patients expect researchers to care about them, too, and this care should be preserved—even amplified—as research and clinical activities are ever more complexly interwoven. Given recent developments in health learning systems, it seems increasingly futile to try to separate research from clinical care along traditional lines. Regulations should be developed that acknowledge the dual roles providers will increasingly occupy as both health professionals and researchers while leaving room for patient preferences—to be told about ongoing research in-person, to have access to more information if desired, to move consent off the page and into interpersonal spaces—and space for realizing that patients *can* express their own preferences, can separate research aims from treatment aims, and can do so better in face-to-face interactions than they can

with consent forms and other contractual kinds of interactions. We can honor the ethical values of respect for patient autonomy, of beneficence, and of non-maleficence by seeking to build trust and informed consent protocols that work for all stakeholders involved and do not simply reflect regulatory concerns.

As our medical spaces change to more deeply accommodate research with the far-reaching capacity to greatly improve health and wellness, we have ripe opportunities to create regulatory oversight that supports, rather than undercuts, the patient-provider relationship. As I have discovered, honoring healthy patient-providers relationships is of paramount importance if we want research to help us keep improving patient outcomes.

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