

Clinical Research with Pregnant Women:

Investigator Insights on Success

Robert Thomas Franceschini, III

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Committee:

Anna Mastroianni

Leslie Meltzer Henry

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Robert Thomas Franceschini, III

University of Washington

Abstract

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Robert Thomas Franceschini, III

Chair of the Supervisory Committee:
Prof. Anna Mastroianni
School of Law

The lack of clinical research in pregnancy negatively impacts the ability to provide therapeutic treatments and preventions to pregnant women. This study explores the experiences of investigators who have successfully conducted clinical research in pregnancy to identify factors that facilitate success. Semi-structured, in-depth interviews were conducted with seven biomedical investigators affiliated with the University of Washington. A content analysis was conducted to extract concepts and themes identified by the investigator participants.

Four major themes were identified from content analysis: investigator motivations for doing research in pregnancy; financial, scientific, design and legal considerations; relationships; and qualities of a successful investigator. These categories of themes were then analyzed to identify eight factors that enhance the likelihood of successful research in pregnancy. This pilot study identified factors that contribute to successful clinical research with pregnant women. Future research will expand the analysis of investigators' experiences and add examination of the experiences of IRB-affiliated individuals and ethics consultants who have distinct insights into the ethical and legal dimensions of research in pregnancy.

Table of Contents

- I. Introduction 5**
- II. Methods 6**
 - A. Study Design 6**
 - B. Identification of Articles, Studies and their Investigators 7**
 - C. Recruitment..... 8**
 - D. Data Collection 9**
- III. Results 10**
 - A. Data Analysis 10**
 - B. Findings 10**
 - 1. Investigator motivations for doing research in pregnancy 10
 - 2. Financial, scientific, design and legal considerations 11
 - 3. Relationships 20
 - 4. Qualities of successful investigators 23
- IV. Discussion 24**
 - A. Factors that enhance the likelihood of success 25**
 - 1. Strong relationships with other investigators and IRBs 25
 - 2. Clinical care and research environment conducive to conducting research in pregnancy
25
 - 3. Proficiency with human subjects research regulations and acceptance of the legal
environment..... 26
 - 4. Respect for IRB as facilitator and protector rather than barrier 27
 - 5. Transparency along the entire research pathway..... 27
 - 6. Attentiveness to risk-benefit balancing 27
 - 7. Valuing pregnant women’s perspectives and ensuring due consideration of their needs 28
 - 8. Personal commitment to research with pregnant women..... 29
 - B. Limitations 29**
- V. Conclusion 30**
- VI. Acknowledgements 31**
- VII. References 31**
- VII. Appendix..... 33**

I. Introduction

The scientific evidence base for the use of therapeutic treatments and preventions in pregnancy is lacking. Scholars have noted and measured this evidence gap, and they have also reported on a global and domestic scarcity of clinical trials that include pregnant women (Lyerly et al, 2008; Shields & Lyerly, 2013). This evidence gap in clinical research not only burdens health care providers in seeking to provide therapeutics to their pregnant patients but endangers the health of pregnant women and their potential offspring (Baylis, 2010).

The research enterprise has been historically reticent to include pregnant women in clinical trials since the 1960s. One reason cited is the collective memory of thalidomide's tragic consequences for fetal development and diethylstilbestrol's birth defects, which resulted from clinically prescribed drug use during pregnancy (Prout & Fish, 2001).¹ Studies have identified other perceived barriers to conducting research in pregnancy. These barriers include the difficulties in interpreting research regulations, particularly the subpart of U.S. regulations addressing the inclusion of pregnant women in research, and the ethical complexities of weighing risks and benefits for the woman and the fetus (Krubiner et al. 2016; van der Zande et al., 2016).² In addition, liability risk and financial disincentives are perceived as inhibiting both private and public funding for research in pregnancy (Krubiner et al., 2016; van der Zande et al, 2016; Greenwood, 2010). Yet further studies have explored the role of various actors that influence the conduct of research in pregnancy, such as attorneys and institutional review boards (IRB) (Ells & Lyster, 2016; Mastroianni et al., 2017). Nonetheless, U.S. investigators are conducting important research with pregnant women around the globe.

¹ The irony of the tragedies of thalidomide and diethylstilbestrol is that adverse fetal development and birth effects could have been at least mitigated had the drug profiles in pregnancy been fully researched.

² The U.S. Department of Health and Human Services regulations specific to the protection of pregnant women, fetuses and neonates in research ("Subpart B" 45 C.F.R. §§ 46.201-46.207) require that interventions or procedures that do not hold out the prospect of direct benefit to the pregnant woman or fetus can pose no greater than "minimal risk" to the fetus.

Although studies have explored the conduct of research in pregnancy, few, if any, studies have sought to understand how investigators successfully conduct clinical research in pregnancy. This pilot study seeks to identify factors that may facilitate successful clinical research with pregnant women by analyzing the experiences of academic researchers who have conducted and published clinical research in pregnancy. All investigators are affiliated with one academic research institution, the University of Washington (UW).

II. Methods

A. Study Design

This study draws on phenomenology theory, which seeks to describe the common meaning of individuals' lived experience of a phenomenon (Creswell, 2013). Phenomenology was selected as the most appropriate guiding theory because a prior hypothesis was that investigators affiliated with the same institution may have similar experiences carrying out their research. This was specifically thought to be the case with regard to study approvals, the training and research environment, and the investigator outlook on how research in pregnancy can and should be carried out. In following a phenomenological approach, the study sought to describe the investigators' common understanding of what it means to successfully conduct research in pregnancy. Semi-structured, in-depth interviews were used to gain insights into investigators' perspectives on their research. The UW was chosen as the institutional locus of the study to control for institutional factors that may affect the conduct of clinical research. These factors include review by the same IRB and a shared research environment and professional network of investigators. Additionally, selection of this institution facilitated recruitment, in-person data collection, and snowball sampling.

The UW Human Subjects Division determined this study to be exempt from IRB review (STUDY00001010). All participants provided oral consent to participation in the study and to the use of their titles and research backgrounds in publications or presentations. Any responses that participants requested remain confidential were omitted from research findings and have not been referenced in this manuscript.

B. Identification of Articles, Studies and their Investigators

Investigators were considered to have successfully completed a clinical study involving pregnant women if they had recently authored a peer-reviewed clinical research article involving pregnant women participants. Specifically, investigator inclusion criteria required: (1) authorship of a PubMed indexed article; (2) article published within a recent five year period; (3) article reported results of a clinical study involving pregnant women; and (4) study approved by a UW IRB committee.

An adapted version of PRISMA was applied to identify articles, studies, and ultimately their investigators, for interviews (Liberti et al., 2009) (See Appendix). PubMed was used to identify eligible peer-reviewed articles. A search was performed on October 14, 2016 with the following search terms: (((("pregnant"[Title/Abstract] OR "pregnancy"[Title/Abstract]) AND Clinical Trial[ptyp] AND "last 5 years"[PDat])) AND University of Washington[Affiliation]). This search produced 49 results.

Abstracts were screened (n=49) and were excluded (n= 28) if: the study was not a randomized controlled trial, a nested study within a randomized controlled trial, or a pharmacokinetic study; the intervention was not a pharmaceutical drug, device or other product (including vitamin supplements); or where pregnancy was only an endpoint whose incidence was

measured but where pregnancy-related outcomes were not assessed. Abstracts were not excluded based on the condition or health status studied.

Full-text articles were then assessed (n=21) and excluded (n= 6) if: the University of Washington Human Subjects Division (IRB) did not approve the study protocol; the UW-affiliated investigator was no longer at the UW; no pregnant women were enrolled or monitored in the study; or the UW-affiliated investigator was a laboratory pathologist.

Authors with an affiliation with the University of Washington (n=23) were identified from the 15 remaining articles. The biomedical research areas of those articles included: HIV (n=11), influenza (n=1), breast cancer (n=1), tetanus/diphtheria/pertussis (n=1) and pre-eclampsia (n=1).

C. Recruitment

Six investigators were contacted via email to participate in the study. These investigators were chosen to represent at least one author from each study (several articles were from the same study). Five investigators responded affirmatively and were able to participate within the study timeframe. Two investigators were recruited using snowball sampling upon the recommendation of two other investigators, for a total of seven investigator interviews. Those two investigators were among the 23 identified through the earlier screening and assessment process

Investigators who participated in the study have a total of 169 years of research experience since receiving their terminal degrees, with a range of 14 to 36 years. Five investigators were women and two were men. Five investigators primarily study HIV; one primarily studies hypertension, preeclampsia and obstetric pharmacology; and another primarily studies clinical pharmacology in pregnancy and lactation. Collectively, the investigators who participated in the study represent three schools at the University of Washington (Medicine;

Pharmacy; and Public Health) and hold primary and secondary appointments in a total of eight departments within those schools: Biostatistics; Epidemiology; Global Health; Medicine; Pharmacy; Obstetrics and Gynecology; Pharmacology; and Pharmacy.

D. Data Collection

Seven investigators were interviewed using in-depth interviews to explore their experiences conducting research with pregnant women. Interviews were conducted using an interview guide consisting of five open-ended questions, and responses were probed for clarification or illumination of concepts discussed by the investigators. Interviews generally followed these five questions; however, some questions were not asked of every participant due to time constraints and to allow study participants to direct the conversation.

Figure 1. Interview questions for the investigators

- 1. Could you describe what prompted you to conduct research with pregnant women?*
- 2. Could you describe your experiences getting approvals to proceed with your research with pregnant women?*
- 3. What factors do you think enhance the likelihood of successfully conducting studies with pregnant women?*
- 4. Could you describe what advice or guidance you would give others who want to conduct research with pregnant women?*
- 5. Were there any documents or individuals you found particularly helpful during any phase of your research in ensuring that your research with pregnant women was ultimately conducted and reported?*

Interviews were conducted in-person in the investigators' offices at the University of Washington Health Sciences Complex and at Harborview Medical Center in Seattle, WA.

Interviews lasted between 30 and 60 minutes, were recorded using an Olympus voice recorder,

and were transcribed verbatim. Notes were taken during interviews to record insights and observations.

III. Results

A. Data Analysis

Content analysis of investigators' responses took place in several steps. Full-text transcripts were first read to grasp investigators' perspectives on research with pregnant women. Transcripts were then hand-labeled to identify themes or concepts that could potentially serve as codes. Hand-labeled themes and concepts were then compiled in a list, grouped by categories, and combined to account for redundancies in concepts or themes. The codebook was then developed and its contents examined by thesis advisors. Once the codebook was finalized, codes were entered into ATLAS.ti as a code list and grouped as families according to categories. Text fragments of all seven transcripts were then labeled in ATLAS.ti.

B. Findings

Four categories of investigators' experiences conducting research with pregnant women were identified: (1) investigator motivations for doing research in pregnancy; (2) financial, scientific, design and legal considerations; (3) relationships; and (4) qualities of a successful investigator.

1. Investigator motivations for doing research in pregnancy

Almost all investigators (n=6) identified motivations for conducting research in pregnancy. Several (n=3) identified the HIV epidemic of the 1980s and 1990s as a motivation for conducting research in pregnancy, and specifically, HIV research in pregnancy:

I spent a lot of time in Africa before I went to medical school in the '90s when the HIV epidemic was really bad... And it's not an exaggeration to say that people were dying all over the place. I mean, I worked at a

very small NGO and I was there for four months in the summer. And we had three funerals just among our staff. So it was a really difficult time, people were passing away. That was something personal that I was involved in. I knew the name of every baby who died in the study. I knew the mother's name. Often I had to sit in clinic when the mother came in and cried and told us that her baby had died. I saw babies die who were old. You expected the very young infants to a certain degree in developing countries, but an eight-month old kid is a big kid, and I saw that kid every single month for their entire life. I saw them die. That makes a big difference. (Investigator 5)

Many investigators (n=5) also identified a perceived knowledge gap in treatment during pregnancy as a motivation for conducting their research:

... We have diseases that are common that we don't know how to take care of: preeclampsia, pre-term birth. There are huge health care outcomes, quality of life outcomes, economic outcomes, and we don't have answers about how to take care of them. So that's how you get answers: you do research... (Investigator 6)

This perceived knowledge gap in treatment during pregnancy was the result of a personal experience in pregnancy for one investigator:

I did my training with the intent of studying drugs that are used in the transplant population: rejection and drug interactions and that kind of thing. Then I got pregnant with my first child and was really ill and realized at that time that there was almost nothing known about drugs and pregnancy. And when I got pregnant with my second child, there was still nothing known. (Investigator 1)

Lastly, several investigators (n=3) noted post-graduate training as influencing their decision to do research in pregnancy:

The first study was done in the early nineties, and I came on as a post-doc... to be the statistician on a study randomizing women to either breastfeed or formula feed—HIV-positive women—to breastfeed or formula feed their infant. Because we didn't know how HIV was transmitted in breast milk and needed to answer that question. So that was kind of the first, how I got into HIV research... (Investigator 4)

2. Financial, scientific, design and legal considerations

a. Financial considerations

Investigators (n=4) identified funding considerations related to the conduct of research with pregnant women. With regard to obtaining funding, two investigators specified that federal agencies almost exclusively fund their research, primarily the National Institutes of Health. One of those investigators noted that private industry has not funded and would be unlikely to fund her research, although industry has assisted in related data analytics on occasion (Investigator 1).

Another investigator described how she addresses funding limitations for studies in pregnancy in low-resource settings. She described the need to calculate the financial costs of different aspects of her studies and prioritizing certain costs over others:

... [A]s HIV testing has progressed, and you can get more real time answers as to whether a pregnant women is HIV infected or not, the balance between thinking about costs, [] thinking about testing infants and thinking harder about how to do that in-country and do it quickly to get the answer to the mother more quickly.... What are you going to have to do if you do one thing? What are you going to have to cut back on? Because these budgets are always limited. I think with most of the investigators I work with, they almost always hit that limit of what an R01 will pay. So you're balancing laboratory costs, clinic costs, testing costs, and so which of those things do you have to give up to build this other piece up? (Investigator 4)

b. Evidence gathered before, during and beyond the study

All investigators (n=7) mentioned attentiveness to how and what type of evidence is gathered as crucial to the success of research in pregnancy. Several investigators (n=5) specifically described gathering evidence before a clinical study as crucial to success. One identified the collection of social science and biomedical data as helpful to getting his study approved by drug regulatory authorities and IRBs:

We of course brought in all the information we had gathered from the qualitative information, the clinical information, the clinical safety information, the quantitative survey information—bring that all in [to the IRB and drug regulatory authorities] and say, “We have evidence it works, we have evidence it’s safe, we have evidence that it’s safe for use in women in early pregnancy, and we have the desire for use from couples.” This all argues that it’s worthwhile and safe and right to continue the evaluation in pregnancy. (Investigator 2)

Another investigator mentioned evidence gathering before a study to make the case for her research in the face of controversy. She used a contraceptive study (in non-pregnant women) as an example of how she has a practice of describing potentially controversial issues early in the IRB review and approval process, and does not wait for the IRB to raise the issue:

... I didn't go around the controversy. I mentioned it head-on. I said, “As everyone knows [Depo-Provera] is controversial.” I cited the literature saying that it might have an increased risk of HIV. I also cited the literature saying that removing DMPA might cause an increase in maternal mortality from lack of contraception options. So I referenced the pros and cons of the controversy. (Investigator 5)

One investigator identified animal studies as crucial for pharmacokinetic studies in

pregnancy when a therapeutic benefit has not yet been proven in pregnancy:

When you're giving a drug, you can't just give any old drug to a pregnant woman unless you've had all that background animal work done. (Investigator 1)

Several investigators (n=5) also mentioned the importance of gathering and monitoring different types of evidence during studies. One investigator mentioned how evidence gathering during a study can affect safety monitoring not just for the fetus, but also for pregnant women and the clinical standard of care used to treat them:

... [W]e randomized pregnant women to two different ARV regimes. They're really old ones, they're not used at all anymore, but we randomized women to see which of those might be better in terms of maternal health outcomes and then looking at infant outcomes. Very early on into it, we realized pregnant women on one of the drug arms, the nevirapine arm, were having much higher hepatic toxicity. I mean, so much so that we stopped the study early, we wrote a report... It changed standard practice, and it was part of the demise of nevirapine. So it was really about safety. It's like, we can't just be giving pregnant women these drugs because we think they're going to be better for infant prevention. You have to make sure that they're safe. (Investigator 3)

That same investigator mentioned ways of structuring study protocol during the IRB review and approval process to gather evidence in studies that do not deliberately target pregnant women. She first noted that investigators should weigh the risks and benefits of taking a woman off an intervention once she becomes pregnant. She then mentioned the importance continuing to gather evidence on pregnancy outcomes from women taken off study due to pregnancy:

... Oftentimes [investigators] say somebody will come off study if they're pregnant. Really the right thing to do may be to take them off whatever the intervention is—and you need to think about the risks and benefits of taking them off the intervention, particularly if it's therapeutic—but they absolutely should stay on-study, and they should get pregnancy outcomes. To expose somebody in early pregnancy, you want to know what happened with that. (Investigator 3)

One investigator mentioned the utility of conducting social science research during a prevention study (pre-exposure prophylaxis for HIV prevention) to understand participant perspectives:

[I]t helped considerably to do a lot of behavioral-social science work, both qualitative and quantitative, while the studies were ongoing. While the trials were ongoing, there were nested or ancillary, whatever you want to call it, qualitative work to understand some of the motivators for prevention, for being together as a couple, for PrEP use in particular. (Investigator 2)

Investigators (n=4) mentioned the importance of considering how evidence gathered in a

study might contribute to or affect future studies in pregnancy. One investigator described her experience conducting an observational pharmacokinetics and pharmacodynamics study for a drug regulatory authority, and how that evidence could be used incrementally to support proposals for later and more complex research. For her, that study's design was intentional and formative, as it contributed an evidence base for conducting an interventional study in pregnancy for that same regulatory authority:

Once you've done that, going into the next situation, you have even more evidence because not only have you done pharmacokinetic, pharmacodynamics studies but in a pregnant population. So the next one with [a drug regulatory agency] was more challenging because instead of studying a drug the patients were going to get anyway, we were studying patients that we were going to give them a drug for research purposes. (Investigator 1)

One investigator described his consideration of a woman's reproductive lifecycle in a foreign, low-resource setting, beyond her participation in the study. In his example, he accomplished this by monitoring women into breastfeeding who were taken off the intervention due to pregnancy:

We also... did a study on breastfeeding women at the same time [as the on-protocol intervention] to produce that same type of information about safety after pregnancy, because I think the whole package is important, because women in this setting [a foreign setting] spend a fairly large fraction of their reproductive years either pregnant or breastfeeding a child. And I think that total package together brought together in pieces—but in pieces thinking together and thinking forward all the time—what's necessary to be able to now implement that intervention on a wide scale without big gaps in knowledge and without big concerns because of those gaps. (Investigator 2)

c. IRB sophistication and knowledge

All investigators addressed the IRB's level of sophistication and knowledge in approving studies in pregnancy. One investigator addressed the experience of the UW IRB in approving research in pregnancy:

I think we have an IRB that's very comfortable doing reviews on pregnancy. They're helpful in guiding language. There are other IRBs that find that they just don't want to do anything, like a community hospital IRB, they're not as sophisticated, and pregnancy is just too complicated. (Investigator 6)

Another addressed her experience serving on an IRB committee and how that has affected her work as an investigator and her advocacy for colleagues trying to conduct research in pregnancy:

I decided pretty early on in my academic career, at that early stage when you have to sign up to be on a

committee, I was like, “I definitely need to learn more about the human subjects side,” so I decided to start serving on the IRB. I feel like I learned a lot from that process, and I was also able to help advocate for researchers as well too. So I think mostly, the process has been pretty straightforward. You just have to be clear about what the reg[ulation]s are, and address the committee’s concerns, and as long as your project has the underpinning of you either want to help that group of women specifically or you want to help women in similar circumstances in the future, usually it’s not an issue. (Investigator 3)

d. Study design

Almost all investigators (n=6) discussed study design. Several noted the utility of observational studies because of the ease of approval due to the absence of an intervention and randomization. One investigator noted how the decision to undertake an observational study, versus an interventional study, changes the risk-benefit calculation. Specifically, this shifted the regulatory requirement of “minimal risk” needed for study approval because the risk calculation was based upon blood draws, rather than a drug or biologic intervention:

For a drug that a patient is going to be receiving already, that drug isn’t the risk of your study because they’re going to get it anyway. Then only the research procedures themselves become the risks of the study. So if you’re going to do blood drawing or any other procedures on the patient, that cannot add any more than minimal risk. And blood drawing isn’t more than minimal risk. (Investigator 1)

Others (n=3) specifically mentioned their experiences conducting interventional research with a known therapeutic benefit in pregnancy. One investigator described how comparative effectiveness research involving interventions with known therapeutic benefits for pregnant women—in this case, for the treatment of gestational diabetes—affects the study’s risk assessment and the ability to randomize:

...[b]ecause if you don’t treat the gestational diabetes, there are high risks of mortality for the mother and baby, so it’s standard of care to treat them. These drugs have been used in this population, it’s not known which is better or whether the combination is better, so we were able to do this study where we could randomize patients and we could stratify by age as well. And so although you’re giving drugs and the drugs themselves are not minimal risk, the drugs actually decrease the risk of the disease and are considered part of standard of care therapy, so we were able to randomize. (Investigator 1)

Two investigators discussed the process of seeking IRB approval for a study with an intervention lacking a known therapeutic benefit for pregnant women. One described how this issue fostered a thoughtful conversation among the investigators and the three relevant IRBs about how to

mitigate institutional liability risk relating to the inclusion of pregnant or breastfeeding women, or those who might become pregnant during the study:

In... the placebo-controlled trial, we had lots of conversations with participating IRBs, both here at the University of Washington, but most importantly in the two countries where the study was done, about what do we think would be the extent to which we would take on risk in working with populations who could become pregnant, would become pregnant, and were pregnant, and were breastfeeding. (Investigator 2)

e. Relevance of the research question to pregnant women

Investigators (n=6) described the importance to the success of research in pregnancy of generating research questions that are relevant to pregnancy and important to the pregnant women themselves. One investigator described these two considerations:

If it's relevant to the woman and asks a question that women want the answer to, it's going to be so much easier to do it well. (Investigator 3)

Another explained why she thought research questions targeted to the needs of pregnant women make for research that successfully includes pregnant women:

I think about it more around what the research question is. If it's a question that is directly relevant to pregnant women, then the research should be done in that population. I think that problem is when it's a broad research question that affects more than pregnant women and they get excluded. (Investigator 7)

f. Time constraints specific to research in pregnancy

Investigators (n=5) brought up issues surrounding the length of time it takes to carry out a study in pregnancy compared to research in non-pregnant populations, in terms of time to approval, time to completion of study, time to publication of study results, and time to hearing of what other colleagues in the health care field are doing. One investigator noted the longer length of time to IRB approval:

I don't think I've ever submitted a proposal to the IRB and was not able to do the study. Now, does it take longer and more revisions and more attention to the consent form? Sure. (Investigator 6)

Another investigator discussed how, in designing her studies in pregnancy, she tries to create protocols that are attentive to the essential needs of the study and the circumstances of the pregnant or recently pregnant women:

Multiple, 24-hour PK visits, including after delivery... can be very onerous. Or doing things like collecting lots of genital specimens. Nobody likes having pelvic exams. If you're going to collect genital specimens, it should be for a really good reason. Really contained to wherever it is. (Investigator 3)

The same investigator also mentioned the importance of time management for clinician-investigators doing work in pregnancy:

From my side, obviously if I decide I want to create a Hepatitis C protocol in pregnancy, no one's going to give me a bunch of time to do that. I'm going to have to figure out how to get it done in between seeing patients and doing C-sections, and various other things. But if it's important enough to me, I'll do it. It's just a question of, I can't do 20 things, but the one thing at a time, do it well, move onto the next thing. (Investigator 3)

g. Involvement of people outside the research team in research planning

Investigators (n=4) discussed the involvement of people outside the research team in informing decisionmaking before and during the study. One investigator described how she includes the local clinicians and investigators at various study sites in crafting both study design and protocol and in the writing of research publications: "...by the time my project goes to the IRB in [the foreign country] and in the U.S., I feel like it's been vetted by many, many people, and the same with research products" (Investigator 5).

Another discussed the minimal role of pharmaceutical companies in her studies:

The drug companies for the most part do not want to do research in pregnancy because of liability issues. I've been approached by multiple companies to give them advice on how to approach particular research questions or sometimes with respect to study design that they need help with. But for the most part, they don't want to touch it with a ten-foot pole. (Investigator 1)

h. Risk-benefit balancing

All investigators described risk-benefit calculations in some form as integral to design and approval. One investigator described the risk-benefit calculus' importance for the IRB

approval process, and how she disaggregates risks and benefits in her protocols for the pregnant woman and fetus, according to the research regulations requirements:

... [A]ny ob[stetrician] taking care of a patient should be doing a risk-benefit analysis before they prescribe or choose not to prescribe any medication... We just apply the same thing when we approach human subjects applications so they understand the thought process and the way we think about and weigh risks. When we fill out the IRB application and create a consent form, we go through the process and lay out what are the risks to the mother for the disease state, and what are the risks of the medication for the disease state, what are the benefits of the medication for the disease state. And what are the risks of the medication to the fetus for the medication, what's known about it, and that's drawn from the literature. (Investigator 1)

Another investigator described her calculus where the study was designed to benefit the mother but posed risks to the fetus or infant:

I do work in HIV prevention in non-pregnant women, as well and when they become pregnant, what do you do? Most investigational drugs, you take them off because you're concerned about the unborn infant. So I think you always have to think of the dyad—you want benefit for the mother, but what's the risk to the unborn child or the born child, if they're breastfeeding, you have to think of that too. You're always thinking about that dyad in terms of design and protecting both mom and baby. (Investigator 4)

One investigator described his risk-benefit calculation and consideration of minimal risk under federal regulations in studies that pose direct benefit to the woman but not the fetus:³

There are—I'm sure you're aware of regulations around doing research in pregnancy. That's that the potential risks to the mother, the potential benefits, have to outweigh the risk and the fetus can be exposed to no more than nominal risk. In some interpretations, that gets a bit carried away. (Investigator 6)

i. Risk appraisals

With regard to risk, investigators described risks to the pregnant woman (n=7), the infant (n=5), and the fetus (n=4). An investigator noted the importance of considering not just the risks of the condition and the intervention to the fetus, but to the pregnant woman:

... A lot of people, when they think about drugs and pregnancy, they only consider the risks to the fetus, but we don't give drugs to healthy women, right? So you have to be weighing it against what are the risks of the underlying condition that you're treating and in the case of gestational diabetes and the oral agents

³ It should be noted that Investigator 6 specifically referred to “nominal risk,” not “minimal risk.” However, given his description of “nominal risk,” it can reasonably be inferred that he was in fact referring to the regulatory concept of “minimal risk.” This particular investigator referred to “nominal risk” again in a separate portion of the interview where he provided a definition for the concept, stating: “If at the end of the day, the study is safer than driving on the freeway, is safer than everyday life, then it's nominal risk. It doesn't mean there's no risk. It just means it's in the same ballpark as the risks of everyday life.” (Investigator 6)

we use to manage them? They do have some risks but it's much lower for both the mother and the fetus than the disease itself. (Investigator 1)

Several investigators (n=4) mentioned harm to the fetus (n=3), the infant (n=1), or the pregnant woman (n=4), and several (n=4) described issues of safety to the fetus (2), the infant (n=2), or the pregnant woman (n=4).

One investigator discussed how she considers the societal implications of not doing research in pregnancy:

Well, just understanding [that] doing nothing has its own risks and benefits, and so that's the comparison. Not the comparison of this magical "I could give you this drug which may be poisonous, or I could not give it to you." But not giving it to you has its own risks and benefits we need to compare... (Investigator 5)

Similarly, one described the harms of not including pregnant women in research by stating, "by excluding a whole group, you are doing a lot more harm than good" (Investigator 7). She went on to describe downstream harms of exclusion to the woman, fetus, and ultimately, society:

Broadly, I think more the fetus is at risk for harm during pregnancy—direct harm from the intervention or the study itself—and the woman is more protected. And I may be wrong, but I don't think of things changing her physiology in that taking something approved for non-pregnant adults would suddenly be toxic. I do know this happens—nevirapine—but in general that's how I think about it: the harm from the study or the intervention to the fetus. But often I think that's taken out of proportion to the harm that is, ultimately, you know it ends up being harm to the population: down-the-line harm by excluding them. That's how we do research. I'm not saying we shouldn't consider immediate harm. But we need to balance those. (Investigator 7)

j. Benefit appraisals

Almost all investigators (n=6) specifically mentioned benefit, either to the pregnant woman (n=6), the fetus (n=3), the infant (n=3), or society (n=1). One investigator discussed considerations related to the relationship between the pregnant woman and her fetus and how he perceives his work in HIV prevention to offer the prospect of benefit to the woman and the fetus:

... And there's an additional benefit to the infant, because if the mother were to become infected during pregnancy, the chances of transmitting to the infant are even greater if one acquires HIV during pregnancy than if one already has HIV during pregnancy. There's the additional benefit of trying to prevent infection in the infant. (Investigator 2)

k. Investigator knowledge of regulations regarding human subjects research

Several investigators (n=5) described explicitly or implicitly the need for investigators to be familiar with the regulations regarding human subjects research. Two investigators specifically referenced the concept of “minimal risk,” a standard defined in federal regulations on human subjects research, including the subpart related to research in pregnancy. One investigator mentioned knowledge of the regulations by reference to IRB policies, and two investigators mentioned FDA drug regulations for investigational drugs. For example, with specific reference to research in pregnancy, one investigator discussed the need for investigators to know the regulations in research: “Design your studies in ways that take into account all the regulations that must be met in conducting studies in vulnerable populations” (Investigator 1).

l. Liability risks

Investigators also mentioned liability risk to institutions (n=3) and to investigators (n=3). An investigator also discussed the role of the IRB in attending to the safety of research participants and safeguarding the investigator and institution from potential liability:

Because of the vulnerability of the population and the concern that something could go wrong, and that... they don't want the IRB to be shut down, they don't want to end up on the front page of the Seattle Times, and neither do the investigators. So they're just being extra careful to make sure everything is done as properly and completely and safely as it possibly can... [O]ur primary interest is the health and safety of the patients that we study. So the fact that the IRB has that [the health and safety of the patients] as their primary concern, I'm totally good with that. (Investigator 1)

3. Relationships

Nearly all investigators referred to their relationships with other investigators interviewed for this study. Three investigators suggested I speak with Investigator 3, with whom they have a working relationship in clinical care and research settings. Investigator 7 mentioned the role of her mentor in her career development—a mentor with whom she now conducts research—and

Investigator 4 mentioned that she trained and continues to work with Investigator 7's mentor.

Investigators 1, 3 and 6 all mentioned either working relationships with each other or suggested I speak with the other two investigators for this project.

All investigators described the importance to success of fostering relationships with other people, both in and outside of their research networks. Investigators identified several actors important to successfully conducting research in pregnancy, including colleagues (n=6), the IRB (n=6), other investigator participants in this study (n=6), the study participants themselves (n=4), the study team (n=4), mentors (n=4), professional networks (n=3), regulatory authorities (n=3), local communities where research is to take place (n=2), and the male partner (n=2).

Another investigator explicitly noted the importance of “[h]aving a relationship with the IRB. They’re not the enemy.” (Investigator 6) He went on to explain why maintaining a relationship with the IRB is important:

...[I]n the U.S., it has to do with having a relationship with the IRB, their administrators, talking to them about “I have this study I want to do, give me a heads up about what you’re going to need”... [Y]ou have to realize first that they’re trying to do a good job at protecting a vulnerable population. They’re also trying to do a good job protecting the university from outside review and sanction. (Investigator 6)

On the other hand, another investigator described a relationship with colleagues as more beneficial than one with the IRB, stating, “Consulting with the IRB is fine, but the IRB is more of a regulatory role and one has to do a lot of soul searching and discussion with one’s colleagues.” (Investigator 7) Another investigator described the importance of consulting with colleagues in maternal-fetal medicine and neonatology:

... I usually will check in with others as well to get their thoughts on [the feasibility of a study] because one person might feel that something is totally safe but a person who’s more conservative might say, well I wouldn’t go above this dose or I wouldn’t approach that. And I usually also consult with neonatology, and there have been a couple of people in neonatology that I’ve consulted on fetal safety and neonatal safety of drug studies. (Investigator 1)

The role of mentors was also discussed, with one investigator stating:

I also think it's really helpful for developing investigators to have more than one mentor. It's good to have a mentorship committee, or a cohort. So some people are really strong at helping you do this but not that, and some people are good at this. Some people are ideas people, some people are follow-through people. (Investigator 3)

She then described how forging relationships with pregnant women has led her to consider the pregnant woman's point of view in studies:

There are just a lot of examples... where you really have to take the pregnant woman's perspective. Really, you stayed up all night breastfeeding for the last three weeks? Do I really want to make you come in several times? And I have to make sure I get you in and out of clinic as quick as possible, and not keep you here for hours and hours filling out all kinds of forms and questionnaires. (Investigator 3)

Another investigator illustrated how continuous engagement with his pregnant research participants has led him to more fully understand the women's motivations for participating in studies:

...Although these women in general are incredibly motivated to participate, they know what their life is like going through this, they know the uncertainty. And they would like the women, their sisters and daughters, metaphorical sisters and daughters, to have more information when the time comes... (Investigator 6)

An investigator described the importance of working with local communities outside of the United States where she conducts her research in designing her studies:

...[M]ost people wouldn't consider...[the research I do] CBPR [community-based participatory research] but those are the principles I have in mind. Where you're making sure you're not doing something that the community would object to, you want to have that community standard for all the things that you study. (Investigator 5)

One investigator described the potential for the investigator to develop relationships in ways other than in study design and approvals, such as in strengthening the research ethics capacity in foreign, low-resource settings:

In fact, [we] did a lot of work to get local doctors and local ethicists, people local in [the foreign country] trained... to see how the UW does human subjects approvals. And so that's developed into ethics boards and [putting] IRB processes in place. (Investigator 4)

Another investigator described the importance of working with local communities outside of the United States where she conducts her research in designing her studies:

...[M]ost people wouldn't consider...[the research I do] CBPR [community-based participatory research] but those are the principles I have in mind. Where you're making sure you're not doing something that the

community would object to, you want to have that community standard for all the things that you study. (Investigator 5)

4. Qualities of successful investigators

All investigators recognized that certain investigator qualities contribute to successfully conducting research in pregnancy. Qualities identified include entrepreneurship (n=3), confidence (n=3), expertise in their field (n=3), creativity (n=2), resilience (n=2), safety (n=2), trustworthiness (n=2), ambition (n=2), transparency (n=1), time management skills (n=1), and intentionality in actions (n=1).

One investigator traced her contacts from professional networks to her entrepreneurialism in conducting research in pregnancy and treating pregnant women:

It's really about having your ear to the ground, because by the time things are in the [HIV pregnancy] registry, it's like three years out. The Hep[atitis] C drugs will be in the registry five years from now. And nobody's treating co-infected women. And I don't know why they aren't because Hep[atitis] C-positive women who have HIV have a higher transmission rate to the fetus. I'd think you'd totally want to start with them. So there's a really good therapeutic rationale for doing that, and there's a lot of general hesitation in our, among my colleagues to be the first to do something. But that's what research is about. You want to go ahead, be the first to do something, do it in a rigorous way, make sure it's got ethical approval, make sure that patients understand that it's cutting edge and what their alternatives are, and so on. (Investigator 3)

One investigator noted the primacy of resilience in order to conduct research in pregnancy by stating, "First, check to make sure you're very resilient because if you give up easily, this is not the area for you to be doing your research." (Investigator 1) Separately, an investigator described how he continues to conduct research in the face of scarce research dollars for research in pregnancy:

...[I]t's not a favorable research economic question. You can have high impact diseases, and the intervention that you're taking is for a very short amount of time. You're dealing with a finite number of pregnancies some of which have complications and they're only treated for a few months. That's not a health care economics that spurs drug development research. And not to mention that's underappreciated. (Investigator 6)

Another investigator described the importance of "[t]ransparency all along the way, in all the different pieces: interacting with the pregnant women, the nurse, the coordinator, and the clinician who's seeing a woman in a clinical study" (Investigator 2).

IV. Discussion

This study identified four categories of themes that emerged from the investigators' experiences conducting research in pregnancy. This supports the guiding prior hypothesis that investigators who successfully conduct research in pregnancy generally have common experiences doing so. Categories included investigator motivations for doing research in pregnancy; financial, scientific, design and legal considerations; relationships; and qualities of a successful investigator. Analysis of the findings within each category reveals a synergistic relationship among them that can be extrapolated into key factors that enhance the likelihood of successful research in pregnancy. Eight factors are identified and explained below (See Figure 2).

Figure 2. Factors that enhance the likelihood of successful research in pregnancy

- Strong relationships with other investigators and stakeholders involved in research in pregnancy
- Clinical care and research environment conducive to conducting research in pregnancy
- Proficiency with human subjects research regulations and acceptance of the legal environment
- Respect for the IRB as a collaborator and protector rather than a barrier
- Transparency along the entire research pathway
- Attentiveness to complexities of risk-benefit balancing
- Valuing pregnant women's perspectives in research and ensuring due consideration of their needs
- Personal commitment to research with pregnant women

A. Factors that enhance the likelihood of success

1. Strong relationships with other investigators and IRBs

Fostering relationships with various actors inside and outside the research enterprise appears essential to successful research in pregnancy. A strong relationship with IRBs may facilitate research and minimize perceived barriers to conducting research. It may also be related to investigators' concern for the ethical and legal conduct of research and their personal commitment to conducting research with pregnant women. Notable was the role of mentors, colleagues and professional networks to success—the ability to use peers as sounding boards to generate and refine research questions. The combined decades of the investigators' research has likely allowed them to cultivate these relationships and may suggest that seniority and extensive work in the research field is key to the cultivation of these relationships. Though relationships may be crucial specifically to work in pregnancy, they may also be key to the study of disease in any population.

2. Clinical care and research environment conducive to conducting research in pregnancy

The research environment of the institution may also be important to conducting research in pregnancy. The noted relationships among the investigators interviewed for this study suggests that the UW has cultivated a positive culture around conducting research in pregnancy. This culture entails an institutional history of training fellows and other investigators in this type of work, thereby simultaneously developing a network of clinicians and investigators who have developed decades of experience exploring issues related to pregnancy. Of the same vein, the culture has produced a history of the IRB conducting and approving their studies. This research environment may also affect the development of several qualities of successful investigators mentioned in the findings, including creativity, ambition and entrepreneurship.

Related to the research environment is the feedback between clinical care and research in producing successful and innovative research in pregnancy. Being physically situated at a research institution with multiple medical centers and clinics treating and studying pregnant women and their conditions allows investigators to engage in both the provision of care and the pursuit of research. This advantage appeared to play a role for those investigators with experiences in both clinical care and research. They noted how their clinical care experiences treating pregnant women inform their research in pregnancy, and how they use their data to inform the care they provide to pregnant women. This feedback also pertains to the investigator pursuing social science research to inform his clinical research, suggesting that rigorous understanding of participant experiences and views may play a role in the conduct of clinical research in pregnancy.

3. Proficiency with human subjects research regulations and acceptance of the legal environment

Investigators evidenced facility and proficiency with regulatory concepts of risk and benefit, and treated the distinct regulatory parameters as one of a number of factors they must address in order to conduct this research successfully. That acceptance of the regulatory environment and facility with complex regulations may be an important factor in ensuring successful research with pregnant women. It is notable that in this investigator population, the concept of legal liability arose infrequently, and when it did, the investigator either acknowledged that the IRB played an important role in protecting research participants, investigators and the institution, or with expressed assumptions on the reason for pharmaceutical companies' lack of interest in funding or conducting studies in pregnancy.

4. Respect for IRB as facilitator and protector rather than barrier

Investigators appeared to have a generally positive view towards the IRB, its role in the design and approval process, and its application of human subjects research regulations. A prior hypothesis had been that the IRB poses a barrier to the success of research in pregnancy due to its interpretation and application of human subjects research regulations. This hypothesis was also thrown into question when investigators noted the important role of foreign IRBs in design and approval. No investigators perceived the IRB as an impediment to conducting research, nor did any perceive the IRB to make overly cautious readings of research regulations. To the contrary, investigators noted working relationships with the IRBs at the UW or partner institutions in foreign countries. The ethics capacity building that one investigator noted could also enhance the relationship with foreign IRBs.

5. Transparency along the entire research pathway

Several investigators touched on the concept of transparency as being a factor in success. Multiple investigators shared their experiences being explicit with IRBs about controversies or potential study risks of their studies. The theme of transparency may also be related to other themes that emerged. For example, recognition of the longer time frame for conducting research in pregnancy may suggest that being open with communities and IRBs about research intentions, risks, and benefits may facilitate research success.

6. Attentiveness to risk-benefit balancing

Careful risk-benefit calculations also appear important to success. Investigators intimated that risk-benefit calculations and appraisals are nuanced and specific to a given study, depending on study design type and whether an intervention was involved.

There were particular differences in how investigators described risk. Whereas those who mentioned minimal risk defined the concept in absolute terms, at other times investigators explained risk generally as relative to the disease state of interest. These conceptions of risk track with the types of studies investigators were describing when discussing risk: risk in a pharmacokinetic study of a drug already prescribed for use by the pregnant woman with blood draws tended to be described in absolute terms whereas risks of an intervention study of a pharmaceutical product were described in relative terms. This may be because drug study risks may require significantly greater justification (on ethics or legal grounds, among others), even if the intervention has already been proven to offer a potential benefit to the pregnant woman or fetus.

With regard to benefit, investigators mentioned the importance of considering benefits both to the woman and to the fetus or infant. For instance, one investigator described how in an interventional study, a known benefit to the pregnant woman could be used to justify the prospect of benefit to the fetus. This was in direct reference to an HIV drug intervention used to treat a pregnant woman that potentially offered the prospect of benefit to the fetus by preventing HIV transmission in pregnancy. Moreover, investigators also mentioned potential societal benefit from conducting research in pregnancy—conducting research in pregnancy is essential for establishing an evidence base for treatment in pregnancy, and importantly not doing research can pose risks to pregnant women (and to her developing fetus) by perpetuating the lack of an evidence base for treatment of pregnant women.

7. Valuing pregnant women's perspectives and ensuring due consideration of their needs

The investigators' experiences conducting research in pregnancy all reveal that situating the pregnant woman and her needs at the center of all decisions regarding a study is a factor in

success. This factor was mentioned along the entire research pathway, from the starting point of initial conception of research questions to beyond a study's completion. For example, investigators noted the role of the pregnant woman and her therapeutic needs as important to developing research questions for investigation. Investigators also focused on pregnant women when discussing how they devise their study design with other investigators, the IRBs, and the woman's own community and partner. Even when discussing evidence gathering and monitoring, investigators noted how the accumulation of more evidence leads to more treatments and preventions for pregnant women and their potential offspring and enhances the effectiveness and extent of eventual studies in pregnancy. All of this suggests that investigators should perceive the pregnant woman as a stakeholder in the research and not merely as a research subject.

8. Personal commitment to research with pregnant women

A personal commitment to their work appears to animate investigators' career decisions to conduct research in pregnancy. As the data suggests, investigators are drawn to this type of research because of personal experiences during the HIV epidemic, a perceived knowledge gap for treating pregnant women, experiences in post-graduate training, or personal experiences during pregnancy. Also, the considerations of lengthier time to completion of studies and grant funding realities suggest that investigators who do this work are partially motivated by altruism and a belief in the importance of the work.

B. Limitations

There are several limitations to this study. The findings and discussion of this study may not be generalizable to the wider experiences of investigators conducting research in pregnancy, given that the investigators interviewed were limited to those with affiliations with the

University of Washington. Recruitment may also be biased, given that several investigators identified in the selection process were not contacted or recruited for participation in the study. Recruitment was limited to seven investigators because it was estimated that saturation would be reached with five to ten study participants. More participants will be recruited for the post-pilot phase of this study.

Data transcription and analysis may have been biased by the use of a single reviewer to transcribe, analyze and code the data collected. This was only partially accounted for by having thesis advisors review and refine the codebook. Additionally, the reporting of primary data may also be biased due to the selection of excerpts from investigator experiences. However, the reporting of descriptive statistics of the number of investigators experiencing a similar concept is meant to account for this limitation. Opportunities for further research include interviews with investigators at other institutions, with UW IRB staff and members, and with women who participate in clinical research in pregnancy.

V. Conclusion

The purpose of this study was to understand factors that contribute to the successful conduct of clinical research in pregnancy. This pilot phase achieved that purpose by collecting, categorizing and analyzing the experiences of investigators affiliated with the University of Washington that are conducting this work around the world. The findings of this study highlight a number of factors that support the successful conduct of research in pregnant women, using one academic institution as the focal point.

Future research will explore the breadth of investigator experiences within a larger institutional data set. This analysis will be supplemented with experiences of others at the institution that have provided substantial guidance in the design, review and approval of studies

in pregnancy, including IRB staff members, the IRB director and ethics consultants. The additional experiences of this non-investigator population will provide yet more insights into the legal and ethical dimensions of research in pregnancy.

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VII. Appendix

PRISMA 2009 Flow Diagram

Identification

Screening

Eligibility

Included

