

**THE PARTICIPATION OF PREGNANT WOMEN  
IN CLINICAL RESEARCH:  
IMPLICATIONS FOR PRACTICE WITHIN THE U.S.  
PHARMACEUTICAL INDUSTRY**

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## **ABSTRACT**

**KRISTINE E. SHIELDS: The Participation of Pregnant Women in Clinical Research:  
Implications for Practice within the U.S. Pharmaceutical Industry  
(Under the direction of John E. Paul)**

Background: The treatment of medical conditions complicating pregnancy is challenged by a serious lack of information about the safety and effectiveness of the medications used by pregnant women. To improve our knowledge of what constitutes the most effective therapy, we conduct systematic research. Research for pregnant women, however, is challenging. The U.S. pharmaceutical industry is the leading conductor of clinical research, yet there is a dearth of published information from industry regarding pregnant women and drug studies. The extent of their exclusion has not been quantified, nor has its rationale been articulated. Industry input will be solicited when FDA releases its new guidance document on pregnant women in clinical research.

Methods: To quantify the proportion of pharmaceutical company-sponsored studies that exclude pregnant women, we reviewed exclusion criteria from Phase IV trials posted on ClinicalTrials.gov from October 2011 – January 2012. To articulate the rationale for exclusion, we conducted key informant interviews (KIIs) with representatives from industry and related organizations.

Results: Of 368 studies in which pregnant women could appropriately participate (drugs in FDA pregnancy categories A, B, or C and conditions that could occur during pregnancy), 94% excluded pregnant women. KIIs found that exclusion is primarily based on beneficence - the desire to avoid causing harm. Other issues include perceived risk of litigation, scientific validity, risk to drug approval and company reputation, and increased study complexity. Lack of advocacy, lack of regulatory requirement, and historic precedent are other barriers. However, KIIs also revealed that industry stakeholders agree with other advocates that pregnant women and their fetuses are at a higher risk of adverse medical consequences if they are not included in clinical trials than if they are included – and that opportunities exist within industry for more inclusive practices.

Conclusion: We verified the perception that pregnant women are largely excluded from clinical studies and found that industry has both practical rationales for exclusion and recommendations to improve inclusion. This study adds industry's perspective to the dialogue on the barriers to, and opportunities for, a rational inclusion of pregnant women in clinical research to ultimately improve evidence-based treatment decisions for pregnant women.

To my inspiration:

My parents, Peter and Margaret Volpinari,

And my children, Nicholas, Chloe, and John

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## PREFACE

### Introduction to the Principal Investigator:

In October 2010, I participated on the organizing committee for the Drug Information Association's Maternal and Pediatric Drug Safety Conference held in Bethesda, MD.<sup>1</sup> One of the invited speakers, Anne Drapkin Lysterly, presented a session entitled "How and When Should Pregnant Women Be Allowed to Participate in Clinical Trials?" She divulged that the pharmaceutical industry had not been included in recent meetings of thought leaders on this topic. She suggested that it was time for the industry to be brought into the dialogue.

The pharmaceutical industry is uniquely positioned to play a meaningful role in this debate because of its influence on the conduct of clinical research in the U.S. where it funds more studies than any other organization including the National Institutes of Health.<sup>2</sup> The industry is responsible for the research design, the research protocol, the inclusion and exclusion criteria, and the conduct of each of the studies they sponsor. Therefore, the pharmaceutical industry has a major influence on the extent to which pregnant women are included in clinical research studies.

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<sup>1</sup>Drug Information Association (DIA). (October 13-14, 2010.) Maternal and Pediatric Drug Safety Conference, Bethesda, MD.

<sup>2</sup>Pharmaceutical Research and Manufacturers of America. (2010). Press Release: R&D investment by U.S. biopharmaceutical companies reached record levels in 2010. Washington D.C. Retrieved on March 15, 2011 from <http://www.phrma.org/media/releases/rd-investment-us-biopharmaceutical-companies-reached-record-levels-2010>

In my 10-year practice as an OB/GYN Nurse Practitioner, I cared for pregnant women in need of medical intervention. In my 12-year role as the director of a pharmaceutical company's pregnancy registry program, I worked in the industry and championed the collection and communication of safety information about drug exposures during pregnancy. I wrote and presented widely on the topic. With this background in obstetrical practice and pregnancy research in the pharmaceutical industry, I felt that I was uniquely positioned to raise and discuss the issue of pregnant women in clinical trials with my industry colleagues.

Knowing many stakeholders involved in the issue - in industry, at FDA, in medical practice, and within academia - I would be able to access and articulate the issues involved from multiple perspectives. By raising the issue with industry colleagues, and by presenting this study's findings, I felt that I would be able to facilitate the dialogue and encourage industry's participation in the debate. I agree with the efforts being made to broaden pregnant women's access to clinical research and believe that progress will not be made without the participation of the pharmaceutical industry. This dissertation was conducted to contribute to these efforts and to promote multidisciplinary dialogue.

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## LIST OF ABBREVIATIONS

ACE – Angiotensin-converting-enzyme

ACOG – American College of Obstetricians and Gynecologists

BIO – Biotechnology Industry Organization

CDC – U.S. Centers for Disease Control and Prevention

CFR – Code of Federal Regulations

CIOMS – Council for International Organizations for Medical Sciences

COPD – chronic obstructive pulmonary disease

DES – diethylstilbesterol

EMA – European Medicines Agency

FDA – U.S. Food and Drug Administration

FDAMA – Food and Drug Modernization Act

HIV – Human Immunodeficiency Virus

IOM – Institute of Medicine

IPA – International Pharmaceutical Abstracts

IRB – Institutional Review Board

KII – Key Informant Interview

NIH - National Institutes of Health

OB/GYN – Obstetrics and Gynecology

OPRU – Obstetric-Fetal Pharmacology Research Unit

PD - Pharmacodynamics

PDUFA – Prescription Drug User Fee Act

PhRMA – Pharmaceutical Research and Manufacturers' Association

PI – Principal Investigator

PK - Pharmacokinetics

SPH – School of Public Health

UNAIDS – Joint United Nations Programme on HIV/AIDS

UNC – University of North Carolina

WHO – World Health Organization

# Chapter 1

## Background & Significance

### A. Significance of the Issue and Problem Statement

*"The lack of drug studies in pregnancy constitutes a major public health problem."*<sup>3</sup>

"Each year over 400,000 women in the U.S. confront significant medical illness while pregnant."<sup>4</sup> In addition to pregnancy-specific complications like gestational diabetes and pre-term labor, medical conditions that occur in non-pregnant women occur in pregnant ones as well, including psychiatric illness, cancer, and infectious diseases. These conditions can have a devastating impact on the health of the pregnant woman and on the well-being of her fetus. The safe and effective treatment of medical conditions complicating pregnancy is challenged by a serious lack of information on the safety and effectiveness of medications used to treat illness. Women's health care practitioners lament that the "current evidence base for the care of pregnant women facing illness is widely regarded as deplorable."<sup>5</sup>

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<sup>3</sup> Zajicek, A. & Giacoia, G.P. (2007). Clinical pharmacology: Coming of age. *Clinical Pharmacology and Therapeutics*, 81(4), 481-482.

<sup>4</sup> Little, M.O., Faden, R., Lyerly, A.D., & Umas, J. (April, 2009). Workshop: The Second Wave: Toward the responsible inclusion of pregnant women in medical research. Georgetown University, Washington, D.C. Retrieved from <http://kennedyinstitute.georgetown.edu/secondwave/>

<sup>5</sup> Lyerly, A.D., Little, M.O., & Faden, R.R. (2011). Reframing the Framework: Toward fair inclusion of pregnant women as participants in research. *The American Journal of Bioethics*, 11(5), 50-52, p. 51.

The only way to improve our knowledge of what constitutes the most effective therapeutic interventions in these unfortunate circumstances is to conduct systematic research. Yet, despite the recommendations of subject matter experts like the U.S. Food and Drug Administration [FDA]<sup>6</sup>, the Institute of Medicine [IOM],<sup>7</sup> the Council for International Organizations of Medical Sciences (CIOMS),<sup>8</sup> and the American College of Obstetricians and Gynecologists (ACOG)<sup>9</sup> to include pregnant women in drug research studies, exclusion is the norm. Without information from research studies, clinicians, pregnant women and their supporters are left to make treatment decisions based on past practices, educated guesses, and gut feelings. We can and should do better than this.

In the U.S., the pharmaceutical industry is the leading funder and conductor of clinical research studies.<sup>10</sup> Yet there is a dearth of published information from the industry regarding pregnant women and drug studies. The extent of pregnant women's exclusion has not been quantified, nor has the industry's rationale for their exclusion been articulated.

In order to improve the treatment of medically compromised pregnancies, proponents (such as ethicists, women's health advocates, and health care providers in academia,

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<sup>6</sup>Feibus, K. & Goldkind, S.F. (May 17, 2011) Pregnant women and clinical trials: Scientific, regulatory, and ethical considerations. Oral presentation at the Pregnancy and Prescription Medication Use Symposium, Silver Springs, MD.

<sup>7</sup>Mastroianni, A.C., Faden, R., & Federman, D. (Eds). (1994). Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine. Washington, DC: National Academy Press.

<sup>8</sup>Council for International Organizations of Medical Sciences. (2002). International ethical guidelines for biomedical research involving human subjects. Retrieved on April 17, 2011 from [www.cioms.ch](http://www.cioms.ch).

<sup>9</sup>American College of Obstetricians and Gynecologists. (2005) Maternal decision making, ethics, and the law. ACOG Committee Opinion No. 321. *Obstetrics and Gynecology*, 106, 1127-37.

<sup>10</sup>Wendler, D. (Spring, 2009). Ethics of Clinical Research. In Zalta, E.N. (Ed.), *The Stanford Encyclopedia of Philosophy*. Retrieved April 26, 2011 from <http://plato.stanford.edu/archives/spr2009/entries/clinical-research/>



government, and the health care system) want a change in practice towards a rational inclusion of pregnant women in clinical research. In order to accomplish this change, the current attitudes and practices of the pharmaceutical industry need to be better understood.

The purpose of this concurrent mixed methods study was to better understand the U.S. pharmaceutical industry's practices and attitudes about the inclusion of pregnant women in clinical research. (To ensure focus and feasibility of completion, the study was limited to the U.S. pharmaceutical industry.) In this study, I quantified the proportion of pharmaceutical company-run studies that excluded pregnant women by reviewing relevant studies' exclusion criteria posted on ClinTrials.gov from October 2011 through January 2012. I also explored the attitudes of key opinion leaders in the U.S. pharmaceutical industry and related organizations, using qualitative interviews to identify key themes regarding the justification for exclusionary practices and the opportunities for inclusive ones.

The results of the study will serve to inform the debate on proposals to change current practices in the U.S. pharmaceutical industry to broaden the inclusion of pregnant women in clinical studies when appropriate. The findings provide support for modifications of research protocols' inclusion/exclusion criteria, institutional review board (IRB) practices, and regulatory guidance. Alternative research designs and other legal, regulatory, and public policy solutions are addressed. Improved maternal-infant health outcomes resulting from improved knowledge of medication toxicities gained from clinical studies in human pregnancies are the ultimate goal.

## **B. Background of the Issue**

*"Pregnant women... are best protected through responsible inclusion in research, not broad-based exclusion from it."<sup>11</sup>*

### **1. Federal Regulations**

As with research practices in general, guidelines regarding women's participation in research have evolved over time. Following the tragic outcomes related to the use of understudied but approved products by pregnant women in the 1960's, particularly diethylstilbesterol (DES) and thalidomide, federal regulations were changed to exclude women of childbearing potential from clinical trials. As the benefits of inclusion in research studies became more evident during the AIDS crisis in the 1980's, women began to advocate against their exclusion from studies. They began to question the accuracy of data derived from studies performed on men when applied to women. Through activism and advocacy, the regulations evolved until even pregnant women were permitted to participate in clinical trials. The current U.S. policy regarding the inclusion of pregnant women in federally funded research is codified in 45CFR46 Subpart B,<sup>12</sup> also referred to as The Common Rule (see Table 1.1).

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<sup>11</sup>Johns Hopkins Berman Institute of Bioethics. (Oct 5, 2009). Press Release, Research News: Second Wave Case Statement.

<sup>12</sup>Code of Federal Regulations, Title 45, Vol. 1. (October 1, 2009). U.S. Government Printing Office via GPO Access [Cite: 45CFR46], 140-143. Retrieved from <http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi>

**Table 1.1 Current Federal Policy on the Inclusion of Pregnant Women in Research**<sup>13</sup>

<p style="text-align: center;">TITLE 45--PUBLIC WELFARE</p> <p>PART 46_PROTECTION OF HUMAN SUBJECTS</p> <p>Subpart B Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research</p> <p>Sec. 46.204 Research involving pregnant women or fetuses.</p> <p>Pregnant women or fetuses may be involved in research if all of the following conditions are met:</p> <p>(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;</p> <p>(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;</p> <p>(c) Any risk is the least possible for achieving the objectives of the research;</p> <p>(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;</p> <p>(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.</p> <p>(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;</p> <p>(g) For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;</p> <p>(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;</p> <p>(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and</p> <p>(j) Individuals engaged in the research will have no part in determining the viability of a neonate.</p>
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<sup>13</sup>Code of Federal Regulations, Title 45, Vol. 1. (October 1, 2009). U.S. Government Printing Office via GPO Access [Cite: 45CFR46], 140-143. Retrieved from <http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi>.

Essentially, the current regulations state that a pregnant woman may participate in a research study if:

- Studies on animals and non-pregnant women have provided data that help define the potential risk to the mother/baby
- AND the research will benefit either the mother or the baby<sup>a</sup>
- AND the study method provides the least possible risk to the mother/baby
- AND the mother gives consent<sup>b</sup>
- OR the mother and the father give consent<sup>c, d</sup>

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<sup>a</sup> Studies that provide no direct benefit to the mother/baby may be conducted but the risk to the fetus must be minimal

<sup>b</sup> For studies that benefit the mother, the mother/baby, or neither

<sup>c</sup> For studies that only benefit the baby

<sup>d</sup> The father's consent is not needed if he is unavailable, incompetent, incapacitated, or if the pregnancy resulted from rape or incest.

While the Code of Federal Regulations now *allows* for the participation of pregnant women in research studies, it does not *mandate* their inclusion. Thus, the *practice* of including pregnant women in research studies remains uncommon.<sup>14</sup> We know that many research protocols specifically exclude pregnant women<sup>15</sup> but I have been unable to find any analysis on the extent to which they are excluded in the scientific literature.

Of note to this research study, the FDA has on its 2011-2 docket of proposed guidance documents,<sup>16</sup> one entitled, "Pregnant Women in Clinical Trials: Scientific and Ethical Considerations" on the inclusion of pregnant women in clinical trials. The guidance is

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<sup>14</sup>Baylis, F. (2010). Opinion: Pregnant women deserve better. *Nature*, 465, 689-670, p. 689.

<sup>15</sup>Hall, J.K. (1995). Exclusion of pregnant women from research protocols: Unethical and illegal. *IRB: Ethics and Human Research*, 17(2),1-3, p. 1.

<sup>16</sup>FDA's Guidance Document To-Do List. (January 3, 2011). "*The Pink Sheet*".

currently in review at the agency. Although the period of review and the release of draft guidance documents is highly variable, particularly for potentially controversial topics such as this, it is slated for release in 2012.

## **2. The Second Wave Consortium**

In October of 2007, Anne Drapkin Lyerly, an obstetrician/gynecologist and ethicist, then at the Trent Center for Bioethics at Duke University, along with colleagues Margaret Little (Kennedy Institute of Ethics, Georgetown University), Lisa Harris (University of Michigan) and Ruth Faden (Berman Institute of Bioethics, Johns Hopkins University) participated in a panel discussion at the American Society for Bioethics and Humanities annual meeting.<sup>17</sup> The session was entitled, "The Second Wave: A Moral Framework for Clinical Research with Pregnant Women." The panel identified the "lack of an adequate moral framework for guideline development" to be a significant barrier to the inclusion of pregnant women in research – and one that sustains the near-universal presumption of exclusion – to the detriment of maternal and fetal health. (See Chap 3: The Ethical Framework of Clinical Research.)

In 2008, Lyerly, Little, and Faden published a paper entitled, "The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research."<sup>18</sup> The paper highlighted the reasons that pregnant women should be included in research: to gain knowledge about

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<sup>17</sup>American Society for Bioethics and Humanities Annual Meeting. (2007). Panel session: The Second Wave: A moral framework for clinical research with pregnant women. Retrieved Oct. 28, 2011 from <http://www.asbh.org/uploads/files/meetings/annual/pdfs/broch07.pdf>

<sup>18</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22.

how to effectively treat pregnant women and keep the fetus safe, to prevent harm from withholding untested treatment that might be effective, for pregnant women to have the ability to decide for themselves whether to participate in studies, and to have access to the medicines available through research. The authors proposed that the exclusion of pregnant women from a research study should need to be justified – as opposed to the current practice of assuming exclusion unless inclusion can be justified. They proposed that the acceptance of inclusion and the justification for appropriate exclusion should be the norm and would benefit from an articulated ethical framework.

In April of 2009, the three authors, joined by Jason Umans from Georgetown University Hospital, sponsored an invitation-only workshop to discuss the costs of excluding and the barriers to including pregnant women in medical research. Various leaders in the field of women's health care research participated including those in academia (Georgetown, Johns Hopkins, Duke), government (National Institutes of Health [NIH], FDA), and other ethicists, women's health advocates, and health care providers. The workshop sought to design actions to address priority issues and to discover what important information was still missing from the debate.

Two key pieces of missing information related to the industry were identified by the workshop participants: 1) the perception of litigation risk [how influential is it and is it a real risk?] and 2) the role of the pharmaceutical industry [how influential is it in affecting the outcome of the debate?].<sup>19</sup> This research study investigated both issues.

It is worth noting that participation in the workshop was by invitation only and that no one from the pharmaceutical industry was invited. I recognize the need to limit the

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<sup>19</sup> Lyerly, A.D. (Nov. 12, 2010). Personal communication.

number of participants to those who were familiar with the issue. The participation of pregnant women in medical research is a sensitive topic that could be easily misunderstood and misconstrued by external audiences, particularly those with specific agendas regarding fetal protection. Describing the negative impact of non-participation is complex and is not easily captured in sound bites. Workshop sponsors may have desired to limit the participants to those who understood the issues a priori and who could contribute to formulating actions that would further the agenda, including a plan to bring industry on board. However, I fear that the lack of an invitation to industry may be perceived as 1) a presumption of an adversarial position by industry and 2) a missed opportunity to acknowledge, educate, and involve a major stakeholder in the debate.

The Second Wave Consortium is not the only group of stakeholders who promote the need to improve our capacity to perform research during pregnancy. A commentary addressed to the OB/GYN community in the *British Journal of Obstetrics and Gynecology* concluded that, "there needs to be a serious and ongoing debate about therapeutic research in the pregnant population and a consensus needs to be reached as to what levels of risk might be considered reasonable."<sup>20</sup>

The debate is not limited to the U.S. but is currently being conducted globally. In fact, several documents from international agencies whose raison d'etre is the promulgation of

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<sup>20</sup>Lupton, M.G.F., & Williams, D.J. (2004). The ethics of research in pregnant women: Is maternal consent sufficient? *British Journal of Obstetrics and Gynecology*, 111, 1307-1312, p. 1308.

ethical standards for research activities, implicitly and explicitly promote the inclusion of pregnant women in clinical research.<sup>21</sup>

Guideline 17 of the 2002 *International Ethical Guidelines for Biomedical Research Involving Human Subjects* of the Council for International Organizations of Medical Sciences (CIOMS)<sup>22</sup> states: “Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the foetus and their subsequent offspring, and to their fertility.”

UNAIDS/WHO Guidance Point 9<sup>23</sup> states: “Researchers and trial sponsors should include women in clinical trials in order to verify safety and efficacy from their standpoint, including immunogenicity in the case of vaccine trials, since women throughout the life span, including those who are sexually active and may become pregnant, be pregnant or be breastfeeding, should be recipients of future safe and effective biomedical HIV prevention interventions. During such research, women’s autonomy should be respected and they should receive adequate information to make informed choices about risks to themselves, as well as to their foetus or breastfed infant, where applicable.”

Stakeholders in the debate about pregnant women's expanded access to inclusion in clinical research are shown in Figure 1.1. I have illustrated what I believe to be their interests in, and influence on, the issue. Of course, pharmaceutical companies have their own stakeholders – stockholders, employees, product consumers, regulatory agencies worldwide, the U.S. tort system – many of whom have competing interests.

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<sup>21</sup>Macklin, R. (2010). The art of medicine: Enrolling pregnant women in biomedical research. *The Lancet*, 375, 632-633.

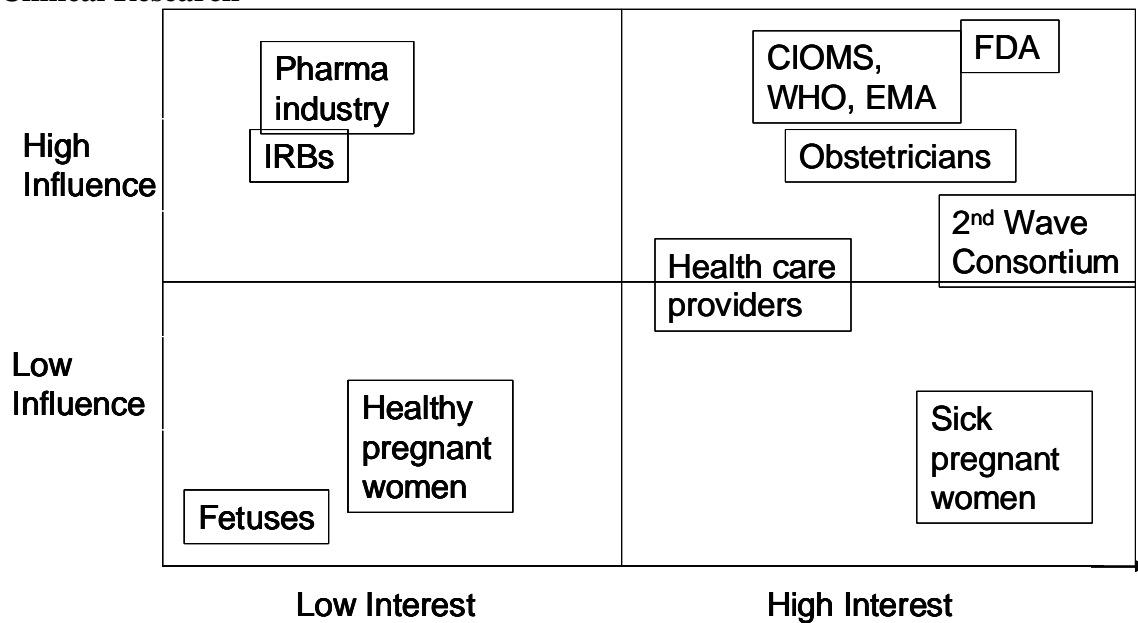
<sup>22</sup>Council for International Organizations of Medical Sciences. (2002). *International ethical guidelines for biomedical research involving human subjects*. Retrieved on April 17, 2011 from [www.cioms.ch](http://www.cioms.ch).

<sup>23</sup>UNAIDS/World Health Organization, Joint United Nations Programme on HIV/AIDS. (2007). *Ethical considerations for biomedical HIV prevention trials: Guidance document*. Geneva. Retrieved from [http://data.unaids.org/pub/Report/2007/jc1399\\_ethical\\_considerations\\_en.pdf](http://data.unaids.org/pub/Report/2007/jc1399_ethical_considerations_en.pdf)



I don't believe that any individual stakeholder would disagree with the goal of providing health care providers and pregnant women with accurate information about the benefits and risks of treatment during pregnancy while minimizing research risks. But the self-interest of each group should be considered in the search for acceptable solutions. As proponents seek to create guidelines for the responsible inclusion of pregnant women in research, it is critical that the pharmaceutical industry articulate its perspective so that all issues and opinions are available for consideration and debate, fully illuminating opportunities for, and barriers to, better-informed decisions and policies. The evolution of safer and more inclusive research designs, regulations, and health care practices may result from this information sharing.

**Figure 1.1 Influence and Interest of Stakeholders in Pregnant Women's Participation in Clinical Research**



\*CIOMS = Council for International Organizations of Medical Sciences,  
 WHO = World Health Organization, EMA = European Medicines Agency

### 3. Consequences of the lack of information

Studies indicate that over 60 percent of pregnant women are prescribed one or more drugs (not including vitamins) during their pregnancy.<sup>24,25</sup> Inadvertent fetal exposure to acute or maintenance medication by women who do not yet realize that they are pregnant occurs frequently as about half of all U.S. pregnancies are unplanned.<sup>26</sup> But we have little data on the safety and efficacy of most medications when they are used during pregnancy. A recent study found that safety in pregnancy was unknown for over 80% of the 468 drugs marketed in a recent 20-year period due to insufficient human data.<sup>27</sup> This leaves the clinician and the patient not knowing how to interpret the little data that do exist - whether to take a potentially effective medication or not; the effect it may have on the woman, the fetus, or the pregnancy; or whether or not to terminate a pregnancy based on the exposure. Nor is it always apparent what the negative consequences will be if she doesn't take a medication, takes less of a medication, takes a different medication, or discontinues a medication.

In my experience conducting pregnancy registries in a pharmaceutical company, I have spoken to women who had been advised by their physicians to consider terminating a pregnancy during which they had inadvertently used a medication or received a vaccine. None of the medications involved were suspected of causing birth defects. The desire to

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<sup>24</sup>Andrade, S.E., Gurwitz, J.H. & Davis, R.L. (2004) Prescription drug use in pregnancy. *American Journal of Obstetrics and Gynecology*, 191, 398-407.

<sup>25</sup>Glover, D.D., Amonkar, M., Rybeck, B.F. & Tracy, T.S. (2003). Prescription, over-the-counter, and herbal medicine use in a rural obstetric population. *American Journal of Obstetrics & Gynecology*, 188(4), 1039-1045.

<sup>26</sup>Henshaw, S.K. (1998). Unintended pregnancy in the United States. *Family Planning Perspectives*, 30:24-29.

<sup>27</sup>Lo, W.Y. & Friedman, J.M. (2002). Teratogenicity of recently introduced medication in human pregnancy. *Obstetrics & Gynecology*, 100, 465-473.

decrease their liability risk if the infant was born with a birth defect is a potential motivation for such advice – but this is speculative. The number of women so advised and the number of pregnancy terminations resulting from inadvertent exposure to medication during pregnancy is unknown.

Experimental drugs with unknown teratogenic potential would rarely be tested on pregnant women in the first trimester. “For humans, the teratogenic period is relatively short, lasting from implantation of the embryo in the uterus, which occurs 5 to 7 days after conception, until the 8<sup>th</sup> week of human development...”<sup>28</sup> Unfortunately, however, this is the most common timing of inadvertent pregnancy exposures to marketed drugs – prior to the mother’s suspicion of pregnancy at her first missed menstrual period.

Overall there is an approximate 3 per cent risk of having a baby with a birth defect.<sup>29</sup> Most of the causes of these congenital anomalies are unknown and medication exposures are known to induce a very small per cent.<sup>30</sup> In fact, the vast majority of drugs and vaccines do not cause fetal harm.<sup>31</sup> Preclinical animal testing has evolved greatly since the tragic impact of thalidomide and DES and, with one exception, all drugs that cause birth defects in humans have been shown to induce defects in animals as well.<sup>32</sup> However, it remains difficult to

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<sup>28</sup>Frederiksen, M.C. (2008). Commentary: A needed information source. *Clinical Pharmacology & Therapeutics*, 83(1), 22-23.

<sup>29</sup>Centers for Disease Control and Prevention. (2011). Birth defects. Washington, DC: Author. Retrieved Oct. 28, 2011 from <http://www.cdc.gov/ncbddd/birthdefects/data.html>

<sup>30</sup>Brent, R.L. (2004). Environmental causes of human congenital malformations: The pediatrician’s role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics*, 113(4), 957-968, p. 958.

<sup>31</sup>Koren, G., Pastuszak, A., & Ito, S. (1998). Drugs in pregnancy. *New England Journal of Medicine*. 338, 1128-1137, p. 1131.

<sup>32</sup>Koren, G., Pastuszak, A., & Ito, S. (1998). Drugs in pregnancy. *New England Journal of Medicine*. 338, 1128-1137, p. 1131.

identify rarely-occurring defects that are caused by drugs. For example, it was only recently ascertained that angiotensin-converting-enzyme (ACE) inhibitors, which have been on the market for over 20 years and were considered to be safe for use in the first trimester of pregnancy, increase the risk for cardiovascular and central nervous system defects.<sup>33</sup> So, while the risk is small for most exposures, the uncertainty remains. This situation leads to fear and potential overreaction by health care providers and pregnant women. Studies indicate that women and their health care providers tend to over-estimate the risk of medication-induced birth defects.<sup>34</sup>

A tragic example of the consequences of such fears is the story told to me by a health care provider whose 7-months-pregnant patient discontinued her asthma medications so as to avoid exposing her baby in utero. She subsequently experienced an acute asthma exacerbation and died. The asthma medications she was taking are recommended to be continued during pregnancy because their risk to the fetus is less than the risk of poorly controlled asthma, as this tragic story illustrates.

It is not only safety information that is lacking; there is a dearth of efficacy information as well. "Many physiological changes that women experience during pregnancy – such as increased plasma volume, body weight, body fat, metabolism and hormone levels – make it impossible to calculate dosage and efficacy information by extrapolating from data

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<sup>33</sup>Cooper, W.O., Hernandez-Diaz, S., Arbogast, P.G., Dudley, J.A., Dyer, S., Gideon, P., ...Ray, W.A. (2006). Major congenital malformations after first-trimester exposure to ACE inhibitors. *New England Journal of Medicine*, 354, 2443-2451.

<sup>34</sup>Koren, G., Bologa, M., Long, D., Feldman, Y., & Shear, N.H. (1989). Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *American Journal of Obstetrics & Gynecology*, 160, 1190-1194.

on men and non-pregnant women."<sup>35</sup> Only by conducting research on women in different trimesters of pregnancy can knowledge of dosing, timing, and efficacy be gained.

The potential impact of a lack of data for drug efficacy during pregnancy is illustrated by the 2002 recommendation by the American College of Obstetricians and Gynecologists (ACOG) of the use of amoxicillin by pregnant women for anthrax post-exposure prophylaxis. Subsequent study, the results of which were published in 2007, showed that this dosage and frequency recommendation was ineffective for pregnant and post-partum women and no studies are available for ciprofloxacin or doxycycline, the alternative antibiotics.<sup>36</sup>

Increased morbidity and mortality, inadequate treatment, the unnecessary termination of wanted pregnancies – these are the consequences of the lack of information about the safety and efficacy of medications used to treat illness during pregnancy.

#### **4. Ethical Issues**

*"There is a tremendous reluctance to include pregnant women in research."*<sup>37</sup>

Concern about fetal safety is the primary motivation against researchers designing studies for pregnant women, against investigators including pregnant women, and against clinicians approaching pregnant women about participating in research studies – as well as the primary reason that pregnant women themselves decline to participate.

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<sup>35</sup>Baylis, F. (2010). Opinion: Pregnant women deserve better. *Nature*, 465, 689-670, p. 689.

<sup>36</sup>Andrew, M.A., Easterling, T.R., Carr, D.B., Shen, D. Buchanan, M., Rutherford, T., Bennet, R., Vicini, P., & Hebert, M.F. (2007) Amoxicillin pharmacokinetics in pregnant women: Modeling and simulations of dosage strategies. *Clinical Pharmacology & Therapeutics*, 81(4), 547-556.

<sup>37</sup>Kennedy Institute of Ethics. (2010). The Second Wave workshop: Toward the responsible inclusion of pregnant women in medical research. Retrieved Oct. 28, 2010 from <http://kennedyinstitute.georgetown.edu/about/news/secondwave.cfm>

Clinical trials have traditionally excluded pregnant women from participation due to this concern. But the ethics of this exclusion are subject to challenge due to the consequential lack of information on the safety and efficacy of medications to treat the multitude of medical conditions that occur during pregnancy.

Which leaves us with an ethical conundrum – we want to improve the health of pregnant women and their babies, to do so we need to do research on pregnant women and their babies, to do so might harm pregnant women and their babies, therefore we can't do research to improve the health of pregnant women and their babies. Yet we do research with attendant risks on men and non-pregnant women. This begs the question, has too much emphasis on nonmaleficence in the pregnant population precluded us from achieving the health benefits of scientific research that have accrued to the non-pregnant population?

The dilemma arises from a conceptual evolution in modern (i.e., developed nation's) obstetrical practice. With technological advances that allow health care providers to see, hear, and actually touch the fetus inside its mother's uterus, many have advanced the notion that the fetus is a patient in its own right. Prior to these individualizing capabilities, the mother-fetal dyad was widely considered to be a "patient package" – a unit. The fetus could only be evaluated indirectly - via palpation and measurement of the mother's abdomen, testing of the mother's blood, external fetal monitoring, etc. It wasn't until labor revealed the fetal scalp through the mother's dilating cervix that direct access to fetal blood was possible. The woman was considered to be somewhat of a barrier to be overcome in order to assess fetal status.<sup>38</sup> In that milieu, the dependency of the fetus on the mother and the mother as the

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<sup>38</sup>Rhoden, N.K. (1987). Informed consent in obstetrics: Some special problems. *Western New England Law Review*, 9(9)(1)/6, 67-88.

primary patient was obvious. With the advent of ultrasound, amniocentesis, umbilical cord blood testing, fetal surgery, and perinatology, however, many have advanced the notion of the fetus as a patient in its own right – sometimes as an individual, conceptually separable patient. Technological developments have led directly to the concepts of fetal rights and fetal 'autonomy' in a clinical as well as a political sense.<sup>39,40</sup> Our ethical conceptions evolve and adapt to encompass advances in technology.

Nonmaleficence, the ethical dictate to avoid doing harm, may influence us to include or exclude pregnant women in studies. Beneficence, to do good, may influence us to include or exclude pregnant women in studies. But justice, the "equitable distribution of the burdens and benefits of research,"<sup>41</sup> requires that we find a way to obtain evidence-based knowledge to formulate best practices to treat pregnant women and their fetuses. [For further discussion, see Chapter 3. The Ethical Framework for Clinical Research.]

### **C. Conceptual Framework**

In 1995, John Kingdon proposed a "Policy Window" theory of change in his book, *Agendas, Alternatives, and Public Policies*.<sup>42</sup> In it, he identified three relatively independent issue workstreams whose interactions are required to advance social change. Kingdon called

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<sup>39</sup>Rhoden, N.K. (1987). Informed consent in obstetrics: Some special problems. *Western New England Law Review*, 9(9)(1)/6, 67-88.

<sup>40</sup>American College of Obstetricians and Gynecologists. (2005) Maternal decision making, ethics, and the law. ACOG Committee Opinion No. 321. *Obstetrics and Gynecology*, 106, 1127-37.

<sup>41</sup>Levine, R.J. (1997). Ethics and Regulation of Clinical Research. New Haven, CT: Yale University Press, pp. 67-93. In Weijer, C., Dickens, B., & Meslin, E.M. (1997). Bioethics for clinicians: 10. Research ethics. *Canadian Medical Association Journal*, 156(8), 1153-1157, p. 1154.

<sup>42</sup>Kingdon, J. (1995). Agendas, Alternatives, and Public Policies, 2<sup>nd</sup> ed. New York: Harper Collins College.

the participants in the workstreams "policy entrepreneurs" – people who are "willing to invest their resources in return for future policies they favor."

The three issue "streams," the Problem (recognition) stream, Policy (proposals) stream, and Political (influence) stream, can move along independently until a point in time when they "converge," often due to external forces. This convergence allows the issue and its potential solutions to be recognized across the workstreams. The "window of opportunity," if capitalized on by the entrepreneurs, can put the issue on the political agenda for resolution by the parties involved. The result is the advancement of social policy.

Entrepreneurs in the problem recognition stream identify, describe, and frame an issue as a problem when it may not have been recognized as such before. Problem definitions often have an emotional values component which helps them to get on the agenda for change.

Entrepreneurs in the policy stream contribute potential solutions to a "primeval soup" in which "ideas confront, compete, and combine with each other" and eventually result in policy formulation.<sup>43</sup> The process relies on groups of interested and knowledgeable parties to propose multiple solutions that are both "technically feasible and consistent with policymaker and public values" and the policy entrepreneurs "must possess knowledge, time, relationships, and good reputations."<sup>44</sup>

The political stream is critical to getting the issue on the agenda for solution. The policy entrepreneur "recognizes the problem, attaches an appropriate policy proposal to it,

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<sup>43</sup>Lieberman, J.M. (2002). Three streams and four policy entrepreneurs converge: A policy window opens. *Education and Urban Society*, 34(4), 445.

<sup>44</sup>Stachowiak, S. (2009). Pathways for change: Theories about how policy change happens. *Organizational Research Services*. Retrieved from [http://www.organizationalresearch.com/publications\\_and\\_resources\\_featured.aspx](http://www.organizationalresearch.com/publications_and_resources_featured.aspx)



and floats the policy proposal in various forums"<sup>45</sup> to bring it to the attention of the people with the power to place it on the agenda for change. Astute policy entrepreneurs can recognize the relationships among the event, the problem, and its proposed solutions and connect the streams. The result of the convergence of two or three of the streams is that "a compelling problem is linked to a plausible solution that meets the test of political feasibility."<sup>46</sup>

Kingdon's Policy Window theory of change provides an appropriate framework with which to contextualize the compelling problem of pregnant women's exclusion from participation in clinical research. The release of the new FDA Guidance will initiate the convergence of a problem stream, a policy stream, and a political stream and provide the impetus that opens the "window of opportunity" for change. The issue and its potential solutions will be debated during the FDA call for public comment following its release. Kingdon recommended initiating special studies of social issues, providing indicators of the existence and magnitude of the problem, and promoting constituent feedback.<sup>47</sup> This study provides indicators of the problem and policy options from constituents to the political debate.

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<sup>45</sup>Lieberman, J.M. (2002). Three streams and four policy entrepreneurs converge: A policy window opens. *Education and Urban Society*, 34(4), 445.

<sup>46</sup>Boussaguet, L., Jacquot, S., & Revinet, P. (2004). *Dictionnaire des Politiques Publiques*, Presses de la Fondation Nationale des Science Politiques, p. 217-225. Retrieved Oct. 12, 2011 from [www.metagora.org/training/encyclopedia/Kingdon.html](http://www.metagora.org/training/encyclopedia/Kingdon.html)

<sup>47</sup>Stachowiak, S. (2009). Pathways for change: Theories about how policy change happens. *Organizational Research Services*. Retrieved from [http://www.organizationalresearch.com/publications\\_and\\_resources\\_featured.aspx](http://www.organizationalresearch.com/publications_and_resources_featured.aspx)

#### **D. Aims of the Study**

*"Alignment of vision among sponsors, caregivers, regulators, policy makers, and consumers is needed to ensure that pregnant women and their children are no longer 'therapeutic orphans.'"<sup>48</sup>*

This study sought to add research and scholarship to the debate about the inclusion of pregnant women in clinical trials – one of the aims of the Second Wave Consortium's effort to change the status quo. Another of its aims is to develop an advocacy agenda to raise awareness with lawmakers and influence legislation, which will be addressed in the Plan for Change (Chapter 7).<sup>49</sup>

The study isolates, articulates, and communicates the opinions of selected pharmaceutical industry and related organization representatives about the inclusion and exclusion of pregnant women in clinical research studies. Attitudes and practices identified by speaking to experts who work in, or interact with, the industry, opportunities for, and barriers to, broadening the safe inclusion of pregnant women in clinical research.

The aims of the study were to:

1. Quantify the frequency of the participation of pregnant women in current pharmaceutical company-based studies by accessing the inclusion and exclusion criteria via ClinicalTrials.gov. (The Food and Drug Modernization Act of 2007 mandates that all federally and privately funded clinical trials be posted on the NIH website, ClinicalTrials.gov.)
2. Raise the issue to selected pharmaceutical industry representatives and related organizations to heighten their awareness of the issue and the debate.

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<sup>48</sup>Zajicek, A. & Giacoia, G.P. (2007). Clinical pharmacology: Coming of age. *Clinical Pharmacology and Therapeutics*, 81(4), 481-482.

<sup>49</sup>Lyerly, A.D. (Nov. 12, 2010). Personal communication.

3. Isolate the concerns of the pharmaceutical industry representatives about including pregnant women in clinical trials to further our understanding of the reasons for, and potential barriers to, their inclusion.
4. Isolate potential opportunities for inclusion of pregnant women in clinical trials from the pharmaceutical industry representatives' perspectives.
5. Ascertain the selected pharmaceutical industry and related organization representatives' perspectives about the industry's role in shaping the debate.
6. Describe the pharmaceutical industry and related organizations' representatives' perceptions of litigation risk.

#### **E. Plan for Change**

*"Now is the time to make important changes to the rules and regulations governing research involving pregnant women..."<sup>50</sup>*

At the conclusion of the study, I will author a "White Paper" on the findings of my research and how they can be applied to the debate on the inclusion of pregnant women in clinical trials.

A White Paper is an authoritative report or guide that helps solve a problem. White papers are used to educate readers and help people make decisions, and are often requested and used in politics, policy, business, and technical fields. Policy makers frequently request white papers from universities or academic personnel to assist policy developers with expert opinions or relevant research.<sup>51</sup>

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<sup>50</sup>Kaposy, C. & Baylis, F. (2011). The Common Rule, pregnant women, and research: No need to "rescue" that which should be revised. *The American Journal of Bioethics*, 11(5), 60-62, p. 62.

<sup>51</sup>Wikipedia contributors. (n.d.). White Paper. Retrieved July 15, 2011 from [http://en.wikipedia.org/wiki/White\\_Paper](http://en.wikipedia.org/wiki/White_Paper)

I will submit the paper to the biopharmaceutical industry's professional groups, PhRMA (Pharmaceutical Research and Manufacturers' Association) and BIO (the Biotechnology Industry Organization), to provide them with a better understanding of the issue, a prelude to what the FDA draft guidelines will likely contain, and – based on the results of this study – potential solutions to the problem.

The paper may serve as an impetus to the creation of a PhRMA- or BIO-based guidance for industry practice and will assist PhRMA, BIO, and individual pharmaceutical companies respond to the call for public comment following the release of FDA's draft guidance, "Pregnant Women in Clinical Trials: Scientific and Ethical Considerations." In addition, I plan to participate in the formulation of PhRMA's response by assisting my employer in the review of PhRMA's proposed response and/or the in the creation of a company-specific response to the FDA's call for comment.

The White Paper will also be shared with the key informants who participated in the study so that they can share the results within their companies and organizations. In that way, the study results will contribute to debate in multiple settings and disciplines.

In addition to the creation of a white paper for industry, I will publish the results of the quantitative study in the peer-reviewed scientific literature. The publication will not only share information to increase awareness and initiate discussion, it will also provide a measure of the prevalence of the exclusion of pregnant women from clinical trials. This measure can then serve as a baseline against which to evaluate the impact of efforts to improve the inclusion of pregnant women in clinical trials.

I am also prepared to speak on the topic at workshops or conferences. Having established a reputation as an industry opinion leader on pregnancy registries, I receive

invitations to speak on the subject of drug safety in pregnancy. I will seek out opportunities to add my voice to the public debate in these forums. The information I gather from the process of conducting the study will also be shared with colleagues via my continued participation in industry groups and organizations that are concerned with maternal health.

## Chapter 2

### Literature Review

#### A. Background and methodology

The Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies was convened by the Institute of Medicine in 1992 at the request of the NIH Office of Research on Women's Health. The committee was asked to investigate, report findings, and propose recommendations to improve the inclusion of women, women of childbearing potential, and pregnant women in clinical studies. Their 1994 report on women and health research made several recommendations<sup>52</sup> including

- that pregnant women be presumed to be eligible for participation in clinical studies and
- that the decision about whether to participate or not should be made by the woman, following the provision and discussion of risk and benefit information by the investigator.

Almost two decades later, these recommendations have not been fully implemented. What arguments support or inhibit the adoption of the IOM's recommendations?

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<sup>52</sup>Mastroianni, A.C., Faden, R., & Federman, D. (Eds). (1994). Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine. Washington, DC: National Academy Press.

**Lit Review question:**

- Why should pregnant women be excluded from clinical trials?
- Why should pregnant women be included in clinical trials?

**Constructs:**

1. Pregnant women
2. Include/inclusion
3. Exclude/exclusion
4. Clinical studies (clinical trials, research studies, drug studies, medical research)

**Methods:**

To locate and obtain literature pertaining to the study constructs, a search for relevant papers was conducted through an electronic search of bibliographic databases available through the UNC Health Sciences Library. The electronic databases searched included Google Scholar, PubMed, and International Pharmaceutical Abstracts. These three data sources were chosen because they encompass the interdisciplinary, medical/clinical, and pharmaceutical domains.

Searches were limited to papers in English about humans that were available from the UNC Health Sciences Library either electronically or in hard copy by request. Retrievals were initially screened by title and abstract for inclusion for further review. Excluded during review, were papers about studies evaluating the treatment of specific diseases or conditions in pregnancy - unless the paper also addressed the reasons for the inclusion or exclusion of pregnant women in the study. Final inclusion was based on a review of the full paper.

Constructs for the initial search included the following terms: pregnant or pregnancy (pregnan\*), and include or inclusion (inclu\*), and "clinical study." These terms were repeated substituting exclude or exclusion (exclu\*) in place of inclusion. Other search terms were tried including pregnan\* and "inclusion criteria", "pregnant in clinical trials", and finally, "inclusion of pregnant" and "exclusion of pregnant" which achieved the best results.

## B. Results

Results from the literature review were initially limited (see Table 2.1) The original concept was too broad and resulted in thousands of papers about clinical studies in pregnancy -- but few addressed the specific topic of why pregnant women should or should not be included in clinical studies. Most of these papers were on the results of clinical and non-clinical studies pertinent to pregnancy. Because the initial searches resulted in thousands of "hits," I limited my review of those findings to the first 50 papers in each. If relevant papers were identified, I continued to search the next 50, and so on. Subsequently limiting the search to the more specific terms, "inclusion (or exclusion) of pregnant" resulted in a higher number of relevant returns.

**Table 2.1 Results of literature review**

Terms: \ Databases:	Google Scholar	PubMed (MedLine)	International Pharmaceutical Abstracts
Pregnan*, inclu*, "clinical trial"	0/1 <sup>st</sup> 50 of 18K	0/1 <sup>st</sup> 50 of 3K	0/22
Pregnan*, exclu*, "clinical trial"	1/1 <sup>st</sup> 50 of 16K	0/1 <sup>st</sup> 50 of 751	0/2
Pregnan*, "inclusion criteria"	0/ 1 <sup>st</sup> 50 of 19K	0/1 <sup>st</sup> 50 of 1444	0/33
Pregnant in clinical trials	2/1 <sup>st</sup> 50 of 185K	9*/1 <sup>st</sup> 50 of 6614 0/2 <sup>nd</sup> 50 of 6614	0/1



"inclusion of pregnant"	49/1 <sup>st</sup> 200 of 258	6/1 <sup>st</sup> 200 of 907	0/1
"exclusion of pregnant"	23/1 <sup>st</sup> 200 of 686	5/1 <sup>st</sup> 200 of 407	0/0

\*All 9 were from the American Journal of Bioethics, May 2011, Issue 11(5).

The references cited in the papers acquired via the review process were also evaluated for pertinent papers not otherwise identified. In addition, papers known to the author were searched for key words, themes, and citations of papers that addressed the literature review questions. These additional papers were included in the review results.

### **C. Discussion**

Using the initial search parameters, I identified papers that were almost exclusively about the results of research studies on the treatment of diseases or conditions in pregnant women. I was at first heartened by the number of studies that involved pregnant women. But on closer look, I noted that relatively few were drug safety and efficacy studies for pregnant women with various disease states. For example, in a quick review of the first 100 papers retrieved from Medline, I noted that 39 were not interventional trials (this group included topics like diet, obesity, exercise, etc.), 26 were about infectious disease (mostly HIV, malaria, and sexually transmitted infections), 10 were about conditions specific to pregnancy, 5 were about alternative therapies (moxibustion, acupuncture), 4 each on diabetes and tobacco or substance abuse, 2 on cancer, and 1 each on other conditions seen in the non-pregnant population (cholesterol, mental health, hypothyroidism, etc.). While not conclusive by any means, this did seem to suggest that the common diseases in the population (heart disease, cancer, cerebrovascular disease, COPD, etc.) that could also affect pregnant women were not being studied in pregnant women. These papers, however, did not meet the goals of

the literature review as they did not discuss the inclusion or exclusion of pregnant women in the studies.

**Of note:** No papers were identified whose topic was the evaluation of a subpopulation of pregnant women in a study that included both pregnant and non-pregnant subjects.

One paper entitled "Eligibility criteria of randomized controlled trials published in high-impact general medical journals" listed "sex-specific conditions such as menstruation, pregnancy, or lactation" in a table under the title, "Poorly Justified Reasons for Excluding Individuals for a Trial."<sup>53</sup> This classification, however, was not accompanied by a numeric value. The paper did not provide a count of the number or the proportion of published trials that excluded pregnant women from their eligibility criteria.

**Of note:** No papers were identified that quantified the exclusion of pregnant women from clinical studies.

The preponderance of papers identified that addressed the subject of the inclusion/exclusion of pregnant women in clinical studies were about the practical and ethical problems associated with their exclusion and the need for their inclusion. Papers defending their continued exclusion were not found. I am speculating that, because exclusion is the accepted status quo, there is little perceived need to discuss, rationalize, explain, or defend it. Whereas interested parties who believe that pregnant women should be included feel the

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<sup>53</sup>Van Spall, H.G.C., Toren, A., Kiss, A., & Fowler, R.A. (2007). Eligibility criteria of randomized controlled trials published in high-impact general medical journals. *Journal of the American Medical Association*, 297, 1233-1240, p.1235.

need to provide their rationale to make their case and to build support for a change in the status quo.

**Of note:** No papers were identified on the topic of why pregnant women are or should continue to be excluded.

Also of interest was the annual publication of the "FDA Guidance Document To-Do List" in the January 3, 2011 edition of "The Pink Sheet,"<sup>54</sup> a weekly publication covering the prescription pharmaceutical industry. On its list of topics the Center for Drug Evaluation and Research is considering for the coming year is the "Responsible Inclusion of Pregnant Women in Clinical Trials." David Kessler, former FDA Commissioner, stated in 1993 that the FDA planned to "develop recommendations... that will facilitate the conduct of trials in pregnant women and result in more such trials."<sup>55</sup> Seventeen years later the regulatory agency has the inclusion of pregnant women in clinical research on its to-do list.

Guidance documents, while not binding, do provide standards and expectations and are closely adhered to by industry. Verified in an FDA presentation on the topic,<sup>56</sup> the draft guidance document is currently in "internal review" at the agency. The length of a review period is variable, so it is not known when it will be released to the public. Once it is released, there is usually a 90-day comment period, where members of the public and other interested parties, including the pharmaceutical industry, can provide feedback to the agency

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<sup>54</sup>FDA's Guidance Document To-Do List. (January 3, 2011). *"The Pink Sheet"*.

<sup>55</sup> Kessler, D.A., Merkatz, R.B., & Temple, R. (1993). Authors response to Caschetta, M.B., Chavkin, W., & McGovern, T. Correspondence: FDA policy on women in drug trials. *New England Journal of Medicine*, 329(24), 1815-1816.

<sup>56</sup>Feibus, K. & Goldkind, S.F. (May 17, 2011) Pregnant women and clinical trials: Scientific, regulatory, and ethical considerations. Oral presentation at the Pregnancy and Prescription Medication Use Symposium, Silver Springs, MD.

about the document. Stated Kessler, "The FDA believes that it is critical to obtain a broad range of views on these matters from the public as well as from experts in the fields of medicine, health care, ethics, and the law, and we are committed to facilitating that exchange."<sup>57</sup> Following the comment period, the document is then re-reviewed and revised within FDA and ultimately, a final guidance document is published. The process can sometimes take several years to complete.

#### **D. Conclusion**

The findings of the literature review support the need for a better understanding of the practice of, and the rationales for, excluding pregnant women from clinical studies. Since no reference was found that quantifies the exclusion of pregnant women from research studies, the assumption that the practice is extensive should be verified. Because no papers were identified solely on the topic of why pregnant women should continue to be excluded from participation in clinical studies, there remains a gap in knowledge. Many of the rationales for excluding pregnant women from clinical trials (discussed below) were extracted from papers on the subject of why we need to include them. Therefore, these findings may be biased and may not reflect the actual thinking of the proponents of exclusion. The literature review supports the need to directly ask those responsible for the exclusion (such as pharmaceutical company sponsors and IRB members) for their reasoning to verify the rationales stated by proponents of inclusion and to make the justifications explicit. Because FDA is preparing a

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<sup>57</sup>Kessler, D.A., Merkatz, R.B., & Temple, R. (1993). Authors response to Caschetta, M.B., Chavkin, W., & McGovern, T. Correspondence: FDA policy on women in drug trials. *New England Journal of Medicine*, 329(24), 1815-1816.

guidance document for industry on the inclusion of pregnant women in clinical trials, it is even more imperative to explore industry's practices and perspectives on the issue. Explicit information will be useful during the public debate on the topic.

## **E. Presentation of Findings**

Findings from the electronic database review with the addition of supplemental papers acquired in the course of researching this topic resulted in the acquisition of many rationales both supporting the inclusion of pregnant women in clinical research and supporting the exclusion of pregnant women from clinical research. I have grouped these rationales into "buckets" to facilitate their presentation and discussion below. See Tables 2.2 and 2.3.

The reason for not including pregnant women in clinical trials is commonly stated as, "Of course, we can't ethically test drugs on pregnant women."<sup>58</sup> Yet there are robust ethical principles that support the arguments both for and against the participation of pregnant women in clinical research. Similar rationales were sometimes cited to support both inclusion and exclusion (e.g., fetal safety, legal risk). Because the topic of this study is laden with ethical issues, I have categorized each identified rationale for and against inclusion by the ethical principle that best applies to the reasoning therein. (See Appendix I: Ethical Principles Invoked For and Against the Inclusion of Pregnant Women in Clinical Research). For further discussion on the ethical framework for pregnant women in clinical research see Chapter 3. Ethical Framework.

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<sup>58</sup>Greenwood, K. (2010). The mysteries of pregnancy: The role of law in solving the problem of unknown but knowable maternal-fetal medication risk. *University of Cincinnati Law Review*, 79, 267-322, p. 274.

## 1. Rationales against the inclusion of pregnant women in clinical research

"Primum non nocere - First, do no harm"<sup>59</sup>

**Table 2.2 Rationales against the inclusion of pregnant women in clinical trials:**

1	The uncertain effect of new drugs on the mother and/or the fetus
2	Litigation risk - Because birth defects are relatively common, they may occur unrelated to the experimental drug exposure, and result in spurious litigation
3	The number of pregnant women needed to participate in the study in order to achieve statistical significance is unachievable
4	Safer study designs are available
5	Alternative treatments are often available
6	Little return on investment
7	Regulations do not require inclusion

Rationale #1: The uncertain effect of new drugs on the mother and/or the fetus.<sup>60</sup> [Ethical rationale: Non-maleficence]

The risk of unforeseen adverse effects on the woman, on the pregnancy, and on the fetus from exposure to the experimental compound is too uncertain to include pregnant women in clinical trials. This risk is one of the most frequently cited reasons for the exclusion of pregnant women from clinical research.<sup>61,62,63,64,65</sup>

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<sup>59</sup>Gillon R. (1985). Primum non nocere and the principle of non-maleficence. *British Medical Journal*, 291, 130.

<sup>60</sup>Mohanna, K. & Tunna, K. (1999). Withholding consent to participate in clinical trials: Decisions of pregnant women. *British Journal of Obstetrics and Gynaecology* 1999, 106, 892-897, p.892.

<sup>61</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22.

<sup>62</sup>American College of Obstetricians and Gynecologists' Committee on Ethics. (2007). ACOG committee opinion: Research involving women. *Obstetrics & Gynecology*, 110(3), 731-736, p. 732.

<sup>63</sup>Beran, R.G. (2006). The ethics of excluding women who become pregnant while participating in clinical trials of anti-epileptic medications. *Seizure*, 15, 563-570.

<sup>64</sup>Weijer, C. (1999). Selecting subjects for participation in clinical research: One sphere of justice. *Journal of Medical Ethics*, 25, 31-36, p. 34.

The FDA acknowledges this issue. The "potential risks of fetal injury, the definition of circumstances under which such risks are justified, and the design of trials that will properly address the risks raise many challenging medical, scientific, legal, and ethical questions," stated David Kessler, former FDA Commissioner, in a 1993 editorial response.<sup>66</sup>

Assurance of drug safety is dependent on the size and composition of the population studied in the clinical trials. (See Appendix II for a review of the U.S. drug development process.) The size of the studies is dependent upon a number of factors including the burden of the disease in the population which affects the number of subjects available to participate. Other considerations include cost and urgency – some studies of diseases for which there are few or ineffective treatments may require smaller sample sizes in order to get the product to patients more expeditiously.

The results of animal studies do not always accurately predict the effects of treatment on human pregnancies.<sup>67,68</sup> While animal reproductive studies are very important in identifying potential teratogenic effects in human gestation, they are not definitive. (A teratogen, from the Greek *teras* meaning monster,<sup>69</sup> is any substance that causes congenital malformations.) Positive findings of teratogenicity in animals do not mean the drug will cause birth defects in humans, and conversely, the absence of teratogenic effects in animals

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<sup>65</sup> Zajicek A and Giacoia GP. Clinical pharmacology: Coming of age. *Clinical Pharmacology and Therapeutics* 2007; 81(4):481-482.

<sup>66</sup> Kessler DA, Merkatz RB and Temple R. Authors response to Caschetta MB et al. Correspondence: FDA policy on women in drug trials. *New England Journal of Medicine* 1993; 329(24):1815-1816.

<sup>67</sup> Macklin, R. (2010). The art of medicine: Enrolling pregnant women in biomedical research. *The Lancet*, 375, 632-633.

<sup>68</sup> Brent, R.L. (2004). Utilization of animal studies to determine the effects and human risks of environmental toxicants. *Pediatrics*, 113, 984-995.

<sup>69</sup> Wikipedia. "Teratology," available at <http://en.wikipedia.org/wiki/Teratology>, accessed 15 July 2011.

does not ensure safety for human fetuses.<sup>70</sup> The number of unintended pregnancies that inadvertently occur in Phase II and III clinical trials is too few to provide accurate data and such subjects are usually disenrolled upon confirmation of the pregnancy. Therefore, we cannot rely on animal testing and preliminary clinical trials to know, or to reassure pregnant women, that it is safe to participate in clinical research.

Rationale #2: Litigation risk - Because birth defects are relatively common, they may occur unrelated to the experimental drug exposure, and result in spurious litigation. [Ethical rationale: Financial stewardship]

An increased risk of both warranted and spurious lawsuits against pharmaceutical companies and researchers is one of the reasons given for the exclusion of pregnant women from clinical studies that is cited by many authors.<sup>71,72,73,74,75</sup> Merton calls this "tort phobia."<sup>76</sup>

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<sup>70</sup>Brent, R.L. (2004). Utilization of animal studies to determine the effects and human risks of environmental toxicants. *Pediatrics*, 113, 984-995.

<sup>71</sup>Lyerly A, Little MO, & Faden R. Perspective: Pregnancy and clinical research. *The Hastings Center Report* 2008; 38(6):[pages unnumbered].

<sup>72</sup>American College of Obstetricians and Gynecologists' Committee on Ethics. (2007). ACOG committee opinion: Research involving women. *Obstetrics & Gynecology*, 110(3), 731-736, p. 732.

<sup>73</sup>Greenwood, K. (2010). The mysteries of pregnancy: The role of law in solving the problem of unknown but knowable maternal-fetal medication risk. *University of Cincinnati Law Review*, 79, 267-322, p. 274.

<sup>74</sup>Charo, R.A. (1993). Protecting us to death: Women, pregnancy, and clinical research trials. *Saint Louis University Law Journal*, 38,135-187.

<sup>75</sup>Kaposy, C. & Baylis, F. (2011). The Common Rule, pregnant women, and research: No need to "rescue" that which should be revised. *The American Journal of Bioethics*, 11(5), 60-62, p. 62.

<sup>76</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 400.



According to population-based research studies, the risk of having a baby with a birth defect is about 3% for major congenital anomalies<sup>77</sup> (structural defects with surgical, medical, or serious cosmetic consequences) and up to 15% for minor anomalies<sup>78</sup> (structural defects that are usually of no surgical, medical, or serious cosmetic consequences<sup>79</sup>). The risk of having a baby with a specific birth defect varies widely – from 1 in 100 infants for heart defects to 1 in 5,000 for rare disorders like anencephaly.<sup>80</sup>

Therefore, if 100 pregnant women were to participate in a clinical study, it is likely that 2 to 4 babies in the study would be born with a major birth defect unrelated to their exposure to the experimental drug provided in the study. However, the mother, the researcher, reviewers of the study findings, and litigators could erroneously conclude that the defect was a result of the exposure. The drug could be incorrectly labeled as teratogenic and the drug's sponsor could be subject to litigation. This misinterpretation could occur even though teratogenic agents are understood to produce specific phenotypic effects depending on the time in gestation of the exposure. In other words, it would be unlikely for a drug to cause a cleft lip in one child and a club foot in another. The injury is usually a characteristic

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<sup>77</sup>Correa, A., Cragan, J.D., Kucik, J.E., Alverson, C.J., Gilboa, S.M., Balakrishnan, R.,...Chitra, J. (2007). Metropolitan Atlanta Congenital Defects Program, 40<sup>th</sup> anniversary edition surveillance report. *Birth Defects Research, Part A: Clinical and Molecular Teratology*, 79(2), 1-120.

<sup>78</sup>Rasmussen, S., Olney, R., Holmes, L., Lin, A., Keppler-Noreuil, K., Moore, C., & the National Birth Defects Prevention Study. (2003). Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Research (Part A)*, 67, 193-201.

<sup>79</sup>Rasmussen, S., Olney, R., Holmes, L., Lin, A., Keppler-Noreuil, K., Moore, C., & the National Birth Defects Prevention Study. (2003). Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Research (Part A)*, 67, 193-201.

<sup>80</sup>March of Dimes. (2011). Birth Defects. Retrieved on May 2, 2011 from <http://www.marchofdimes.com/Baby/birthdefects.html>

effect or cluster of effects that is readily identifiable and reproducible. But lawyers and juries do not always recognize the principles and complexities of teratogenesis.

There is an actual and unfortunate example of this phenomenon. Bendectin, a combination of pyridoxine (vitamin B6) and doxylamine (an antihistamine), which are both available over the counter as separate medications, was approved and is effective for the treatment of nausea and vomiting during pregnancy. Despite having been extensively studied in animal, clinical, and epidemiologic studies<sup>81</sup> with no findings of measurable risk to the developing fetus,<sup>82</sup> the product was withdrawn from the market in 1983 due solely to the burdens of litigation.<sup>83</sup> The product remains on the market in the UK and Canada where it is widely used. In addition to the absence of an effective treatment for hyperemesis gravidarum on the U.S. market, an alleged consequence of this "litigation effect" is the reluctance of U.S. pharmaceutical companies to develop drugs for use during pregnancy. The fact that only two medications – oxytocin and cervidil – have been approved for use in pregnancy since 1962 supports the observation that U.S. pharmaceutical companies are reluctant to develop drugs for the litigious obstetrical market.<sup>84</sup>

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<sup>81</sup>Brent, R.L. (1995). Bendectin: Review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent teratogen-litigen. *Reproductive Toxicology Review*, 9(4), 337-349.

<sup>82</sup>Brent, R.L. (2007). How does a physician avoid prescribing drugs and medical procedures that have reproductive and developmental risks? *Clinics in Perinatology* 2007; 34:233-232, p. 252.

<sup>83</sup>Brody, J. (1983, June 19). Shadow of doubt wipes out Bendectin. *New York Times*.

<sup>84</sup>Wing, D.A., Powers, B., & Hickok, D. (2010). U.S. Food and Drug Administration drug approval: Slow advances in obstetric care in the United States. *Obstetrics & Gynecology*, 115(4), 825-833.

Rationale #3: The number of pregnant women needed to participate in the study in order to show efficacy may be unachievable. [Ethical rationale: Non-maleficence]

Clinical trials are conducted for two primary purposes – to measure efficacy and to evaluate safety. In order to efficiently observe the clinical endpoints that confirm or refute efficacy, the characteristics of subjects permitted to enroll are usually narrowly defined. People with renal impairment, children, and the elderly, for example, are populations that are regularly excluded from initial trials in order to avoid added complexity. Sometimes additional trials for these specific subpopulations are conducted after initial studies on the more homogeneous population have established efficacy. In addition to the safety concerns, the complex physiologic changes associated with the advancing stages of gestation, can justify the exclusion of pregnant women from participation in early clinical trials. Blood volume, renal clearance, body mass index, and hormone levels fluctuate throughout the pregnancy. Trials specifically designed to evaluate efficacy in the pregnant population would be more likely to achieve results that advance evidence-based care, but difficulty with the recruitment and retention of pregnant women may be an obstacle.<sup>85</sup> Baylis cautions that, "Persuading pregnant women to take part in research can be difficult."<sup>86</sup>

Evaluating safety, specifically the potential for a new drug product to induce birth defects, would be even more difficult. "Populations of several thousand would be needed to

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<sup>85</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 400, p.396.

<sup>86</sup>Baylis, F. (2010). Opinion: Pregnant women deserve better. *Nature*, 465, 689-670, p. 689.

assess if the background risk produced by a particular treatment changes the rate of birth defects in general. If we are interested in a specific birth defect that occurs at a rate of 1 in 1000 or fewer, then to demonstrate that a drug does not produce a specific birth defect would require treated and non-treated populations on the order of tens to hundreds of thousands of pregnant women.”<sup>87</sup> Clearly these numbers are not feasible. Therefore, the evaluation of human teratogenicity cannot rely upon clinical trials but requires accumulated data from other sources (see Rationale #4).

Rationale #4: Safer study designs are available. [Ethical rationale: Beneficence]

One of the requirements of 45CFR46 to allow pregnant women to participate in research is that the study is designed to provide the least possible risk to the mother and the fetus. Alternate methods of identifying drug-induced birth defects, including pregnancy registries, case studies, pharmacovigilance, and case-control studies,<sup>88</sup> though not definitive, do not subject pregnant women to the risks of clinical trials, including the risk of receiving a placebo instead of a potentially effective medication. These alternative study approaches are performed after the drug has been approved and is on the market. States Greenwood, "epidemiological studies may be the only way to generate information about both rare birth defects and long-term effects" and these can only be done after the drug is approved and

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<sup>87</sup>Mattison, D. & Zajicek, A. (2006). Gaps in knowledge in treating pregnant women. *Gender Medicine*, 3(3), 169-182, p. 180.

<sup>88</sup>Feibus, K. & Goldkind, S.F. (May 17, 2011) Pregnant women and clinical trials: Scientific, regulatory, and ethical considerations. Oral presentation at the Pregnancy and Prescription Medication Use Symposium, Silver Springs, MD.

marketed.<sup>89</sup> Brent agrees that, "[w]ell performed epidemiology studies are still the best method for determining the human risk and the effects of environmental toxicants."<sup>90</sup> Once basic science, animal testing, and clinical study data have been collected and analyzed and have met FDA standards of benefit/risk analysis acceptable for license approval, then studies of the safety of use in human pregnancy can be performed on marketed drugs. It is safer for the mother and fetus if the safety of a product is as well-established as possible before it is used during pregnancy.

Rationale #5: Alternative treatments are often available. [Ethical rationale: Beneficence]

In fact, we can *never* assure pregnant women that it is safe to participate in clinical research, because we can never prove that a drug is safe in all women at all times. So it is prudent to err on the side of caution and not subject pregnant women and their fetuses to the risks of medical research. Instead, health care providers should continue to use best practice guidelines and the medical literature to prescribe treatment that has been shown to be safe and effective over time. Brent advises that the "obstetrician can avoid product liability litigation by not prescribing drugs that have reproductive risks for the mother or developmental risks for the developing embryo or fetus."<sup>91</sup> Only in situations where the current treatment is not effective and significant morbidity or mortality to the mother or the fetus is likely should we resort to the use of an experimental medication. If the condition is

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<sup>89</sup>Greenwood, K. (2010). The mysteries of pregnancy: The role of law in solving the problem of unknown but knowable maternal-fetal medication risk. *University of Cincinnati Law Review*, 79, 267-322, p. 291.

<sup>90</sup>Brent, R.L. (2004). Utilization of animal studies to determine the effects and human risks of environmental toxicants. *Pediatrics*, 113, 984-995.

<sup>91</sup>Brent, R.L. (2007). How does a physician avoid prescribing drugs and medical procedures that have reproductive and developmental risks? *Clinics in Perinatology* 2007; 34:233-232, p. 252.

not life-threatening or medically significant, we can utilize palliative measures or encourage tolerance of short-term discomfort to ensure that we provide the safest prenatal environment possible to protect the fetus from iatrogenic harm.

Rationale #6: Little return on investment. [Ethical rationale: Financial stewardship]

Pharmaceutical companies are publically held entities that have a responsibility to shareholders to increase profit and decrease loss. We have discussed the difficulties associated with conducting clinical trials on pregnant women. Recruiting, enrolling, and retaining a sufficient number of pregnant women to ensure that their participation will be statistically significant and generalizable to a larger population would be costly and has little hope of success. Even if the benefit of the product can be shown to be greater than the risk of adverse effects, the market of pregnant women is relatively minimal. Therefore, the company may rationally decide that the actual cost of drug development and the potential cost of litigation exceed any potential financial gains.<sup>92</sup> The experience with Bendectin reinforces this case (see Rationale #2). Enrolling pregnant women would expose the pregnant participants and their non-consenting fetuses to medical risk while also exposing the company to significant legal and financial risk.

In addition, "a company that performs studies on one of its already-approved drugs risks 'generating results that could destroy the value of the product rather than enhance it.'"<sup>93</sup> The author of this statement admits, however, that "finding that a drug is unsafe for use

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<sup>92</sup>Charo, R.A. (1993). Protecting us to death: Women, pregnancy, and clinical research trials. *Saint Louis University Law Journal*, 38,135-187.

<sup>93</sup>Eisenberg, R.S. (2005). The problem of new uses. *Yale Journal of Health Policy, Law, & Ethics*, 5, 717-718.

during pregnancy could leave its broader market unaffected."<sup>94</sup> But negative publicity generated by the correct or erroneous finding that a drug causes birth defects, could affect sales, particularly among women of childbearing potential.

Also, limiting enrollment in research studies to non-pregnant women only is less complicated, less costly,<sup>95</sup> and more efficient. The long-term result is that "therapies will become available sooner and cost less."<sup>96</sup>

Rationale #7 – Regulations do not require inclusion. [Ethical rationale: Financial stewardship]

The U.S. regulations (Code of Federal Regulations 45CFR46 Subpart B,<sup>97</sup> or the Common Rule) state that pregnant women may participate in research studies under certain conditions. They do not state that pregnant women must be included in research studies or that pregnant women must be given the option to participate in research studies. The decision as to whether to include or exclude pregnant women from studies is left to the sponsor of the study or the IRB that approves the study. Until regulators make the inclusion of pregnant

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<sup>94</sup>Eisenberg, R.S. (2005). The problem of new uses. *Yale Journal of Health Policy, Law, & Ethics*, 5, 717-718.

<sup>95</sup>Kaposy, C. & Baylis, F. (2011). The Common Rule, pregnant women, and research: No need to "rescue" that which should be revised. *The American Journal of Bioethics*, 11(5), 60-62, p. 62.

<sup>96</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 389.

<sup>97</sup>Code of Federal Regulations, Title 45, Volume 1. (October 1, 2009). U.S. Government Printing Office via GPO Access [Cite: 45CFR46], 140-143. Retrieved from <http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi>

women mandatory, sponsors will continue to avoid the potential legal and financial risks by mandating exclusion.<sup>98,99</sup>

## 2. Rationales for the inclusion of pregnant women in clinical trials

*“Pregnant women get sick and sick women get pregnant”*<sup>100</sup>

**Table 2.3 Rationales for the inclusion of pregnant women in clinical research**

1	To acquire knowledge that improves the medical treatment of pregnant women (and their fetuses)
2	To improve birth outcomes
3	To improve pregnant women's access to the benefits of clinical research
4	To improve the ethical acquisition of information about exposed pregnancies
5	Because regulations do not require the exclusion of pregnant women
6	Excluding pregnant women from participating in medical research is unethical and illegal - and may increase litigation risk
7	To follow the advice of experts in the field of women's health, law, and ethics

Rationale #1 – To acquire knowledge that improves the medical treatment of pregnant women (and their fetuses). [Ethical rationale: Beneficence, Non-maleficence]

Many authors agree that the primary reason to consider the inclusion of pregnant women in research studies is to provide evidence-based treatment guidelines to improve the health of pregnant women and their babies.<sup>101,102,103,104</sup> The lack of information about how to

<sup>98</sup>Baylis, F. (2010). Opinion: Pregnant women deserve better. *Nature*, 465, 689-670, p. 689.

<sup>99</sup>Kaposy, C. & Baylis, F. (2011). The Common Rule, pregnant women, and research: No need to "rescue" that which should be revised. *The American Journal of Bioethics*, 11(5), 60-62, p. 62.

<sup>100</sup>Baylis, F. (2010). Opinion: Pregnant women deserve better. *Nature*, 465, 689-670, p. 689.

<sup>101</sup>McCullough, L.B., Coverdale, J.H., & Chervenak, F.A. (2005). A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. *American Journal of Obstetrics and Gynecology*, 193, 901-907.

<sup>102</sup>American College of Obstetricians and Gynecologists' Committee on Ethics. (2007). ACOG committee opinion: Research involving women. *Obstetrics & Gynecology*, 110(3), 731-736, p. 732.



treat the more than 9 million pregnant women with chronic conditions and the millions more who develop new medical conditions during pregnancy is a significant problem.<sup>105</sup> Because they have not been systematically evaluated in pregnant women, practically all medications used to treat illness during pregnancy are prescribed without FDA approval – essentially off-label use.<sup>106</sup>

Obstetricians, says Lyerly, "care for their patients without meaningful data regarding [drug] safety and efficacy..."<sup>107</sup> "Many physiological changes that women experience during pregnancy – such as increased plasma volume, body weight, body fat, metabolism and hormone level – make it impossible to calculate dose and safety information by extrapolating from data on men and non-pregnant women."<sup>108,109</sup>

Effective medical care is based upon trial and error – and the systematic collection and analysis of data from research conducted in vitro and in vivo over time. Lyerly argues that the whole "purpose of the enterprise of clinical research is to take responsible, limited,

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<sup>103</sup>Greenwood, K. (2010). The mysteries of pregnancy: The role of law in solving the problem of unknown but knowable maternal-fetal medication risk. *University of Cincinnati Law Review*, 79, 267-322, p. 274.

<sup>104</sup>Feibus, K. & Goldkind, S.F. (May 17, 2011) Pregnant women and clinical trials: Scientific, regulatory, and ethical considerations. Oral presentation at the Pregnancy and Prescription Medication Use Symposium, Silver Springs, MD.

<sup>105</sup>Greenwood, K. (2010). The mysteries of pregnancy: The role of law in solving the problem of unknown but knowable maternal-fetal medication risk. *University of Cincinnati Law Review*, 79, 267-322, p. 274-5.

<sup>106</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22, p. 6.

<sup>107</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22, p. 6.

<sup>108</sup>Baylis, F. (2010). Opinion: Pregnant women deserve better. *Nature*, 465, 689-670, p. 689.

<sup>109</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22, p. 5.

and calculated risks in order to garner evidence..."<sup>110</sup> The results of these efforts inform and guide clinical practice. Excluding pregnant women from participation in research studies on new medication results in a lack of knowledge about the effectiveness, the appropriate dosage, and the potential side effects of medication when used during pregnancy – a time when the patient is most concerned about safe and effective treatment.

This lack of knowledge can and does result in a number of adverse consequences for the medically compromised pregnancy. These include withholding treatment, under-treatment, or overexposure of pregnant women and their fetuses.<sup>111</sup> Pregnant women are prescribed medications with "no real basis for predicting their effects."<sup>112</sup> Health care providers may be reluctant to prescribe and pregnant women themselves may discontinue medications – both of which may lead to the lack of effective management of medical conditions during pregnancy. They may lower the dose of the medication thinking that it will decrease the exposure to the fetus. However, this can result in the exposure of a fetus with no therapeutic benefit to the mother. Conversely, standard dosages of some medications may result in overdosing of the pregnant woman due to physiologic changes during gestation. Sadly, lack of knowledge can and does lead to the elective termination of wanted pregnancies based on an unwarranted fear of birth defects following the exposure. I have been told first-hand, and Kass et al. agree, that physicians have encouraged women to terminate pregnancies and pregnant women have terminated otherwise wanted pregnancies based on an inflated

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<sup>110</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22, p. 8.

<sup>111</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22, p. 5.

<sup>112</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 400, p. 382.

perception of the risk of teratogenicity – "despite the fact that fewer than 30 drugs are proven human teratogens"<sup>113</sup> and the percentage of birth defects caused by medication is very low.<sup>114</sup>

Ironically, since women are excluded from much research in an effort to protect the fetus from harm, "significant harm to the child may result from not providing [maternal] treatments. The number of cases in which medications are given inappropriately during pregnancy constitutes a fraction of the number in which indicated therapy is inappropriately withheld."<sup>115</sup> States Lott, "the benefits of barring pregnant women from participating in research may, in the end, harm expecting mothers and their fetuses more than their inclusion in clinical trials."<sup>116</sup>

Rationale #2 – To improve birth outcomes. [Ethical rationale: Beneficence, Non-maleficence]

According to U.S. Department of Health and Human Services, the U.S. ranks 27th among industrialized nations in infant mortality.<sup>117</sup> The infant mortality rate, the rate at which

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<sup>113</sup>Kass, N.E., Taylor, H.A., & Anderson, J. (2000). Treatment of human immunodeficiency virus during pregnancy: The shift from an exclusive focus on fetal protection to a more balanced approach. *American Journal of Obstetrics and Gynecology*, 182(4), 1-5.

<sup>114</sup>Brent, R.L. (2007). How does a physician avoid prescribing drugs and medical procedures that have reproductive and developmental risks? *Clinics in Perinatology* 2007; 34:233-232, p. 233.

<sup>115</sup>Kass, N.E., Taylor, H.A., & Anderson, J. (2000). Treatment of human immunodeficiency virus during pregnancy: The shift from an exclusive focus on fetal protection to a more balanced approach. *American Journal of Obstetrics and Gynecology*, 182(4), 1-5.

<sup>116</sup>Lott, J.P. (2005). Module three: Vulnerable/special participant populations. *Developing World Bioethics*, 5(1), 30-53, p. 48.

<sup>117</sup>U.S. Health & Human Services. (Jan. 13, 2006). Fact sheet: Preventing infant mortality. Washington D.C.: HHS Press Office. Retrieved from <http://www.hhs.gov/news>.

babies die before their first birthday, was 6.9 deaths per 1000 live births in 2003.<sup>118</sup>

Contributing factors include disparities among racial and ethnic groups, congenital anomalies, prematurity, and maternal complications.<sup>119</sup> Medical research is needed to prevent and treat these and other life-threatening conditions.

Healthy babies are dependent upon healthy mothers and healthy pregnancies. Fetal health can be compromised by conditions that affect women in general (e.g., lupus) or conditions specific to pregnancy (e.g., pre-eclampsia) or conditions of fetal origin (e.g., Rh incompatibility). Lack of knowledge about the efficacy or negative impact of various medications constrains treatment options and restricts the abilities of health care providers to provide the best care possible. Birth outcomes are compromised. Therefore, improved fetal safety – often cited as a reason for the exclusion of pregnant women from research – can be just as effectively cited as a justification for the inclusion of pregnant women in research.<sup>120</sup> "Due to the underrepresentation of pregnant women in research, clinicians and women face treatment decisions in the context of a dearth of evidence about how drugs work in pregnant bodies, what doses are safe and effective,...and which drugs pose teratogenic risk for fetuses – a dearth that often leads to reticence to prescribe or take indicated drugs, to the detriment of maternal and fetal health."<sup>121</sup>

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<sup>118</sup>U.S. Health & Human Services. (Jan. 13, 2006). Fact sheet: Preventing infant mortality. Washington D.C.: HHS Press Office. Retrieved from <http://www.hhs.gov/news>.

<sup>119</sup>U.S. Health & Human Services. (Jan. 13, 2006). Fact sheet: Preventing infant mortality. Washington D.C.: HHS Press Office. Retrieved from <http://www.hhs.gov/news>.

<sup>120</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22.

<sup>121</sup>Lyerly, A.D., Little, M.O., & Faden, R.R. (2011). Reframing the Framework: Toward fair inclusion of pregnant women as participants in research. *The American Journal of Bioethics*, 11(5), 50-52, p. 51.

Rationale #3 – To improve pregnant women's access to the benefits of clinical research.  
[Ethical rationale: Justice]

"Restriction of trials to non-pregnant individuals excludes a class of potential beneficiaries and places them at an unfair disadvantage..." state Lyerly et al.<sup>122</sup> Participating in a clinical trial can provide benefits such as "possible therapeutic advantage, better outcome of disease, closer monitoring than in routine practice, getting attention for other ailments, better physical and laboratory health checks, superior physicians, labs, and testing, more contact with the providers, access to contacts for future health information, remuneration, and contributions to society."<sup>123</sup>

To Lupton and Williams, "pregnant women are often treated with drugs that have been superseded in every other branch of medicine...because newer drugs have not been fully investigated in the pregnant population."<sup>124</sup> Clinical trials provide access to current potential advances in medicine and health care practice. Advocates for populations that have been excluded from participation in research studies (i.e., women, people living with HIV/AIDS, and children) have fought for, and succeeded in achieving, inclusion. "The former complete exclusion of fertile women led to more deaths of women with HIV than

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<sup>122</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22, p. 6.

<sup>123</sup>Iber, F.L., Riley, W.A., & Murray, P.J. (1987). Conducting Clinical Trials, New York: Plenum Press. In Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 378.

<sup>124</sup>Lupton, M.G.F., & Williams, D.J. (2004). The ethics of research in pregnant women: Is maternal consent sufficient? *British Journal of Obstetrics and Gynecology*, 111, 1307-1312, p. 1308.

men and eventual revision of exclusionist policies."<sup>125,126</sup> FDA has since revised its restrictions and now believes it is essential to include pregnant women when it is their only way to access potentially life-saving treatments that are under investigation.<sup>127</sup> Including pregnant women in clinical studies would improve their access to new medications and better health care that could improve their health and health of the pregnancy.

Rationale #4 – To improve the ethical acquisition of information about exposed pregnancies. [Ethical rationale: Non-maleficence, Autonomy]

Ruth Macklin states that the most compelling reason for the inclusion of pregnant women in clinical research "is the need for evidence gathered under rigorous scientific conditions, in which fewer women and their fetuses would be placed at risk than the much larger number who are exposed to medication once they come to the market."<sup>128</sup>

For the vast majority of pregnancies in which medications have been prescribed, the birth outcomes are never recorded. According to Berlin, "pregnant women who must take certain medications are essentially participating in an uncontrolled and unmonitored experiment for which the data will most likely never be assessed."<sup>129</sup>

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<sup>125</sup>Cain, J., Lowell, J, Thorndyke, L, & Localio, A.R. (2000). Contraceptive requirements for clinical research. *Obstetrics & Gynecology*, 95(6), 861-866, p. 863.

<sup>126</sup>Edgar, H., & Rothman, D.J. (1990). New rules for new drugs: The challenge of AIDS to the regulatory process. *Milbank Quarterly*, 68, 111-114.

<sup>127</sup>Macklin, R. (2010). The art of medicine: Enrolling pregnant women in biomedical research. *The Lancet*, 375, 632-633.

<sup>128</sup>Macklin, R. (2010). The art of medicine: Enrolling pregnant women in biomedical research. *The Lancet*, 375, 632-633.

<sup>129</sup>Berlin, J.A. & Ellenberg, S.S. (2009). Commentary: Inclusion of women in clinical trials. *BMC Medicine*, 7(56), 1-3.

Hall adds the additional point that "the quality of informed consent is better in a research setting than in the post-marketing environment where prescriptions are written with little instruction and little follow-up is done."<sup>130</sup> "[T]he assumption seems to be that the researcher, or perhaps the IRB member, or perhaps a federal bureaucrat [or perhaps, I would add, the pharmaceutical company] is the best choice to judge the net harm and benefit, risk and advantage, that would result from a pregnant woman's participation in a protocol."<sup>131</sup> Rather, the well-informed pregnant woman, who, by being pregnant, has not lost her ability to evaluate information, judge risk, or make decisions for herself and her fetus, should be the one who decides.<sup>132</sup> .<sup>133</sup>

Lack of knowledge about medication use during pregnancy has led to efforts to collect information about pregnancy outcomes from women who take medications in the post-marketing environment – after the products have been approved. For example, pregnancy registries, studies that evaluate birth outcomes from women who have used approved medications during their pregnancies, have been established for some medical conditions and for some medications but they are usually not required by FDA for new drugs.

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<sup>130</sup>Hall, J.K. (1995). Exclusion of pregnant women from research protocols: Unethical and illegal. *IRB: Ethics and Human Research*, 17(2):1-3, p. 2.

<sup>131</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 399.

<sup>132</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 399.

<sup>133</sup>Beran, R.G. (2006). The ethics of excluding women who become pregnant while participating in clinical trials of anti-epileptic medications. *Seizure*, 15, 563-570.

But, warns Macklin, "surveillance activities...lack the rigor of the scientific gold standard: a prospective, randomized clinical trial in which pregnant women are enrolled."<sup>134</sup>

Rationale #5 – Regulations do not require the exclusion of pregnant women. [Ethical rationale: Justice]

The Declaration of Helsinki states, "Populations that are underrepresented in medical research should be provided appropriate access to participation in research."<sup>135</sup> But the U.S. Common Rule "does little to promote research inclusion for pregnant women."<sup>136</sup>

According to Hall, "there is no regulatory reason for excluding pregnant women from many studies."<sup>137</sup> Historically, women of childbearing potential were excluded from participating in studies based on the study sponsor's overinterpretation of the regulations that had only excluded them from the first and earliest part of the second phase of studies.<sup>138</sup> The exclusion of pregnant women from participation may be, in part, based on a similar misinterpretation.

According to current regulation, pregnant women may be included in studies under certain circumstances. Various study designs have been proposed that can decrease the risk to

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<sup>134</sup>Macklin, R. (2010). The art of medicine: Enrolling pregnant women in biomedical research. *The Lancet*, 375, 632-633.

<sup>135</sup>World Medical Association. (2008). Declaration of Helsinki. Retrieved on Aug. 25, 2011 from <http://www.wma.net/en/30publications/10policies/b3/index.html>

<sup>136</sup>Kaposy, C. & Baylis, F. (2011). The Common Rule, pregnant women, and research: No need to "rescue" that which should be revised. *The American Journal of Bioethics*, 11(5), 60-62, p. 61.

<sup>137</sup>Hall, J.K. (1995). Exclusion of pregnant women from research protocols: Unethical and illegal. *IRB: Ethics and Human Research*, 17(2):1-3, p. 2.

<sup>138</sup>Merkatz, R. (1998). Inclusion of women in clinical trials: A historical overview of scientific, ethical, and legal issues. *Journal of Obstetrical, Gynecologic, and Newborn Nursing*, 27(1), 78-84, pp. 79-80.



the fetus while still providing for the inclusion of pregnant women. In fact, the IOM, in its 2010 report, "Women's Health Research: Progress, Pitfalls, and Promise,"<sup>139</sup> recommends that pregnant women be included unless there is a specific reason to exclude them.

Rationale #6 - Excluding pregnant women from participating in medical research is unethical and illegal - and may increase litigation risk. [Ethical rationale: Justice]

Ethical conduct requires the inclusion of pregnant women in clinical trials, should they choose to participate. Lyerly (2011), citing Mastroianni et al., states that, "access to research, not just protection from its risks, is a constitutive part of the ethical mandates governing clinical research."<sup>140</sup> "Issues of justice," they continue, "are perhaps the most pressing."<sup>141</sup> "Women have the right – the same right as men – to decide for themselves (and, therefore, implicitly, for their potential offspring), whether it is prudent and morally right for them to participate in a given protocol, and women do not lose that right when they become pregnant," agrees Merton.<sup>142</sup>

McCullough et al. question the ethics of treating pregnant in the absence of clinical study data. They state, "Until the risks and benefits of the different treatment options are

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<sup>139</sup>Institute of Medicine Committee on Women's Health Research. (2010). Women's Health Research: Progress, Pitfalls, and Promise. Washington, DC: National Academies Press. Retrieved from [www.nap.edu](http://www.nap.edu)

<sup>140</sup>Mastroianni, A.C., Faden, R., & Federman, D. (Eds). (1994). Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine. Washington, DC: National Academy Press.

<sup>141</sup>Lyerly, A.D., Little, M.O., & Faden, R.R. (2011). Reframing the Framework: Toward fair inclusion of pregnant women as participants in research. *The American Journal of Bioethics*, 11(5), 50-52. p. 51.

<sup>142</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p.388.

quantified and weighed against each other, the continued use of...drugs in these women without a sound evidence-base raises major clinical and ethical concerns."<sup>143</sup>

Writing in *IRB: A Review of Human Subjects Research*, Jacquelyn Kay Hall concluded that "excluding women from publicly paid benefits on the basis of their sex is illegal."<sup>144</sup> "There is no regulatory reason for excluding pregnant women from many studies" she writes, therefore "to exclude all pregnant women from the potential benefits of some protocols is illegal."<sup>145</sup> Vanessa Merton concurs, "[R]esearch sponsors in fact have more to fear in the way of potential liability from the exclusion of...pregnant women...than from their inclusion."<sup>146</sup>

While some view "the automatic exclusion of pregnant subjects as possibly more related to protecting the institution and investigator (from liability) than the subject or her unborn fetus (from possible harm),"<sup>147</sup> an alternative view is that it is the inadequate testing of a drug prior to marketing that increases a company's risk of liability for adverse effects. While there are few reported cases of damages awarded due to injury from inclusion in research, there are a number of cases where damages were awarded for claims of inadequate

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<sup>143</sup>McCullough, L.B., Coverdale, J.H., & Chervenak, F.A. (2005). A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. *American Journal of Obstetrics and Gynecology*, 193, 901-907, p. 902.

<sup>144</sup>Hall, J.K. (1995). Exclusion of pregnant women from research protocols: Unethical and illegal. *IRB: Ethics and Human Research*, 17(2):1-3, p. 1.

<sup>145</sup>Hall, J.K. (1995). Exclusion of pregnant women from research protocols: Unethical and illegal. *IRB: Ethics and Human Research*, 17(2):1-3, p. 1.

<sup>146</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p.369.

<sup>147</sup>Frank, E. & Novick, D.M. (2003). Beyond the question of placebo controls: Ethical issues in psychopharmacological drug studies. *Psychopharmacology*, 171(1), 19-26.

testing.<sup>148</sup> One can imagine the liability claims for thalidomide were it released onto the market today with inadequate evaluation of its teratogenic potential. Had animal testing been performed to today's standards, the teratogenic potential of the drug would likely have been identified. But it is of interest to consider that if pregnant women had been included in the clinical trials for thalidomide, as tragic as the initial cases of birth defects would have been, thousands of cases of the severe limb defects that occurred in exposed children would have been prevented worldwide.<sup>149</sup> Macklin says this "is a simple utilitarian calculation, an appropriate method for decision making when the intention is to decrease the number of individuals exposed to potential harm."<sup>150</sup>

Rationale #7 – To follow the advice of experts in the field of women's health, law, and ethics. [Ethical rationale: Justice, Non-maleficence]

The ACOG Committee on Ethics,<sup>151</sup> the IOM,<sup>152</sup> the International Ethical Guidelines for Biomedical Research Involving Human Subjects of CIOMS,<sup>153</sup> and the FDA<sup>154</sup> have all concluded that pregnant women can be appropriately included in clinical research.

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<sup>148</sup>Mastroianni, A.C., Faden, R., & Federman, D. (Eds). (1994). Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine. Washington, DC: National Academy Press, p. 166.

<sup>149</sup>Lyerly, A.D., Little, M.O., Faden, R. (2008). The Second Wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches in Bioethics*, 1(2), 5-22.

<sup>150</sup>Macklin, R. (2010). The art of medicine: Enrolling pregnant women in biomedical research. *The Lancet*, 375, 632-633.

<sup>151</sup>American College of Obstetricians and Gynecologists' Committee on Ethics. (2007). ACOG committee opinion: Research involving women. *Obstetrics & Gynecology*, 110(3), 731-736, p. 732.

<sup>152</sup>Mastroianni, A.C., Faden, R., & Federman, D. (Eds). (1994). Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine. Washington, DC: National Academy Press.

Respect for the autonomy of patients, beneficence, and justice in the selection of participants are three oft-cited ethical justifications for the inclusion of pregnant women in clinical studies.<sup>155,156</sup> Denying pregnant women the opportunity to enroll in research studies denies them the potential benefits of participation (improved treatment, enhanced medical care) and the opportunity to act altruistically and help other pregnant women.<sup>157</sup>

"Increasingly, research ethics committees are encouraging researchers not to exclude this group of participants from research so long as appropriate safeguards are in place."<sup>158</sup>

In April 2009, subject matter experts in clinical practice, biomedical ethics, NIH, FDA, and others participated in a workshop (the Second Wave Consortium) on the topic of the inclusion of pregnant women in medical research. Their deliberations concluded, in part, with the following statement:<sup>159</sup>

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<sup>153</sup>Council for International Organizations of Medical Sciences. (2002). International ethical guidelines for biomedical research involving human subjects. Retrieved April 17, 2011 from [www.cioms.ch](http://www.cioms.ch).

<sup>154</sup>Feibus, K. & Goldkind, S.F. (May 17, 2011) Pregnant women and clinical trials: Scientific, regulatory, and ethical considerations. Oral presentation at the Pregnancy and Prescription Medication Use Symposium, Silver Springs, MD.

<sup>155</sup>Macklin, R. (2010). The art of medicine: Enrolling pregnant women in biomedical research. *The Lancet*, 375, 632-633.

<sup>156</sup>McCullough, L.B., Coverdale, J.H., & Chervenak, F.A. (2005). A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. *American Journal of Obstetrics and Gynecology*, 193, 901-907.

<sup>157</sup>Mohanna, K. & Tunna, K. (1999). Withholding consent to participate in clinical trials: Decisions of pregnant women. *British Journal of Obstetrics and Gynaecology* 1999, 106, 892-897, p. 892.

<sup>158</sup>Mohanna, K. & Tunna, K. (1999). Withholding consent to participate in clinical trials: Decisions of pregnant women. *British Journal of Obstetrics and Gynaecology* 1999; 106, 892-897, citing Foster, C., (Ed). (1997). Manual for Research Ethics Committees. London: Centre of Medical Law and Ethics, p. 41.

<sup>159</sup>Kennedy Institute of Ethics. (2010). The Second Wave workshop: Toward the responsible inclusion of pregnant women in medical research. Retrieved Oct. 28, 2010 from <http://kennedyinstitute.georgetown.edu/about/news/secondwave.cfm>

"We believe that the current paucity of research on effective and safe treatment of pregnant women's illnesses is unethical. It is unfair and irresponsible to continue a system that compels physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for pregnant women, and for women and the fetuses they carry, to shoulder those risks whenever pregnancy is complicated by illness. As we learned in pediatric and geriatric research, if a population is going to use a medication it must be studied *in* that population. Pregnant women and the children they bear are best protected through responsible inclusion in research, not broad-based exclusion from it."

## Chapter 3

### Ethical Framework

#### I. An Ethical Framework for Clinical Research

Introduction:

Conceptual or theoretical frameworks attempt to connect all aspects of inquiry<sup>160</sup> and provide a structure and a common basis upon which to test hypotheses and justify conclusions. In this study's area of inquiry, where both the pros and cons of the inclusion of pregnant women in research can be argued on the basis of ethical considerations, an ethical framework can assist to provide structure to the debate. A common language that is familiar to and accepted by health care practitioners, researchers, pregnant women, academics, and pharmaceutical industry representatives, will assist stakeholders in the understanding and consideration of ideas, opinions, and options. The proposed ethical framework of clinical research is based upon moral reasoning and ethical concepts that are common to these stakeholders' histories, lived experiences, and values at home and in the workplace.

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<sup>160</sup>Wikipedia contributors. (n.d.). Conceptual Framework. Retrieved June 8, 2011 from [http://en.wikipedia.org/wiki/Conceptual\\_framework](http://en.wikipedia.org/wiki/Conceptual_framework)

## A. Theoretical approaches

Medical practice and clinical research are closely related and share Hippocratic roots, although important differences have been noted. Medical practice focuses on the improvement of an individual's health and well-being, while clinical research attempts to provide knowledge that will improve a population's health and well-being by identifying improved methods to treat, cure or prevent disease.

Medical ethics and research ethics are also closely related and many medical practitioners participate in clinical research. Largent et al. cite technological advances such as electronic medical records, increased demand for evidence-based medicine and comparative effectiveness research, and the recognition that participation in research allows access to new therapies during "evidence development" as reasons for an increased blurring of clear boundaries between research and the provision of care.<sup>161</sup> It needs to be recognized by both the researcher and the participant that, at times, the aims of the research may not coincide with the individual interests of the participant.

To address these and similar issues, the field of research ethics is devoted to the systematic analysis of [ethical and legal] questions to ensure that study participants are protected and, ultimately, that clinical research is conducted in a way that serves the needs of such participants and of society as a whole."<sup>162</sup>

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<sup>161</sup>Largent, E.A., Joffe, S., & Miller, F.G. Can research and care be ethically integrated? *Hastings Center Report*, 41(4), 37-46, p. 38.

<sup>162</sup>Wendler, D. (Spring, 2009). The Ethics of Clinical Research. In Zalta, E.N. (Ed.), *The Stanford Encyclopedia of Philosophy*. Retrieved April 26, 2011 from <http://plato.stanford.edu/archives/spr2009/entries/clinical-research/>

## 1. Principle-based Ethics

Principlism is the ethical approach traditionally applied to the fields of clinical practice, medical research, epidemiology, and public health. Developed in the second half of the 20<sup>th</sup> century by British physician and ethicist, Raanon Gillon,<sup>163</sup> and American ethicists Beauchamp and Childress, it invokes four principles: Respect for Autonomy, Beneficence, Nonmaleficence, and Justice.<sup>164</sup> It is criticized as being too 'Western,' lacking relativity and sensitivity to other cultural perspectives on issues such as liberty, social justice, and the value of life.<sup>165</sup> But it remains the dominant theory applied to clinical practice and research.<sup>166</sup>

### a. The Principle of Respect for Autonomy or Respect for Persons

Twentieth century legal decisions have determined that the authority and power to authorize a health care provider to act on a patient's behalf is vested in the adult, competent patient. Health care providers have the obligation to explain their rationale for recommending an intervention, the risks and benefits of the proposed procedures, alternative interventions they are not recommending, and the reasoning behind these recommendations. The competent adult patient is solely responsible for authorizing the initiation of the intervention.

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<sup>163</sup> Beran, R.G. (2006). The ethics of excluding women who become pregnant while participating in clinical trials of anti-epileptic medications. *Seizure*, 15, 563-570, p. 564, citing Gillon, R., (1985), Philosophical Medical Ethics. Chicester: John Wiley & Sons.

<sup>164</sup> Carter, L. (2002). Major ethical theories. Retrieved March 3, 2011 from University of Queensland Office of Public Policy and Ethics Web site: <http://www.uq.edu/au/oppe>

<sup>165</sup> Carter, L. (2002). Major ethical theories. Retrieved March 3, 2011 from University of Queensland Office of Public Policy and Ethics Web site: <http://www.uq.edu/au/oppe>

<sup>166</sup> Mohanna, K. & Tunna, K. (1999). Withholding consent to participate in clinical trials: Decisions of pregnant women. *British Journal of Obstetrics and Gynaecology* 1999, 106, 892-897, p. 892.



Each patient brings their "unique configuration and history of particular values and beliefs that form the basis for [the] determination of [their] own subjective and deliberative interests"<sup>167</sup> to the situation. Thus the patient is the only one who can make decisions that are relevant in her own context.

But with the complexity and multitude of options in today's medical environment, this deciding cannot occur in a vacuum. Four models of increasingly respectful doctor-assisted patient decision-making were described by Emanuel in 1992: paternalistic, informative, interpretative, and deliberative.<sup>168</sup> In the preferred deliberative model, the caring health care provider teaches the patient about her medical condition and treatment options, discusses both in the context of the values held by the HCP and by the patient, and provides a recommendation based on these factors. In today's environment of overwhelming access to medical information and misinformation, it is imperative that medical providers share perspective as well as knowledge. Kukla characterizes the exchange of knowledge and context by the patient and health care provider as active collaborative knowledge-building.<sup>169</sup> With this assistance, the patient can then make her informed decision based on the consideration of information and value context. Thus respect for autonomy means more than just having the patient make the decision. Today it means respecting the patient's capacity for learning, for evaluating values and context, and for applying these considerations to arrive at a considered decision.

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<sup>167</sup> McCullough, L.B., & Chervenak, F.A. (1994). *Ethics in Obstetrics and Gynecology*. New York: Oxford University Press, Inc., p. 53.

<sup>168</sup> Emanuel, E.J. & Emanuel, L.L. (1992). Four models of the physician-patient relationship. *Journal of the American Medical Association*, 267(16), 2221-2226.

<sup>169</sup> Kukla, R. (2007). How do patients know? *Hastings Center Report*, 37(5), 27-35.

The same principles invoked in the therapeutic environment hold true in the research environment. According to McCullough,<sup>170</sup> the principle of autonomy is a construct of modern Western political philosophy. It is the first principle of the Nuremberg Code,<sup>171</sup> and the Belmont Report.<sup>172</sup> In practical terms, one way of ensuring autonomous choice had been through the provision of informed consent. Spencer defines informed consent as "consent given by a competent person in the light of relevant information and without the presence of any pressure of coercion."<sup>173</sup> Its application to research has been influenced and upheld by legal proceedings that address the independent moral status of people and respect for their self-determination.

#### b. The Principles of Nonmaleficence, Beneficence, and the Double Effect

Though widely quoted and attributed to Hippocrates, the edict, "primum non nocere (first, do no harm)" does not occur in the Hippocratic Oath. A similar statement, "make a habit of two things - to help, or at least to do no harm" occurs in an accompanying text and combines the principles of beneficence – to do good, and nonmaleficence – to do no harm. Nonmaleficence is, according to some ethicists, a corollary of the principle of beneficence

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<sup>170</sup>McCullough, L.B., & Chervenak, F.A. (1994). *Ethics in Obstetrics and Gynecology*. New York: Oxford University Press, Inc., p. 48-9.

<sup>171</sup>The Nuremberg Code. (1947). Retrieved from <http://ori.dhhs.gov/education/products/RCRintro/c03/b1c3.html>

<sup>172</sup>The Belmont Report. (1979). Retrieved from <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

<sup>173</sup>Spencer, A.S., & Dawson, A. (2004). Implications of informed consent for obstetric research. *The Obstetrician & Gynaecologist*, 6, 163-7. In Doyal, L. (1997). Informed consent in medical research. *British Medical Journal*, 314, 1107-11, p. 163.

and not an independent principle on its own.<sup>174</sup> The meaning and import of both principles are obvious: the physician commits to seek interventions on the patient's behalf, the consequences of which are intended to provide benefit and not cause harm. Adherence to these principles in practice encourages the practitioner to utilize her "accumulated scientific and clinical knowledge, skill, and experience" to "protect and promote the interests of the patient."<sup>175</sup> Thus the strength of our beneficence is limited by the "competencies"<sup>176</sup> of our medical judgment at any point in time.

In medical and public health practice there are often situations where an action intended to provide benefit may result in an inadvertent harm – the harm being intentionally less likely to occur or of an acceptable quality or intensity. Examples include mandatory vaccinations that cause adverse effects in some children but benefit many, or surgery to remove an ectopic pregnancy that saves the woman's life but ends the pregnancy. Patients weigh potential benefits against the risk of potential adverse effects when choosing to take medication or consenting to surgery.

The double effect principle recognizes the artificial separation of beneficence from nonmaleficence. It provides criteria to help judge if an intervention is morally acceptable including if 1) the action is morally neutral or good, 2) the intention is to invoke the good effect and not the bad one, 3) the situation is serious enough that the harmful side effect is justifiable, and 4) actions are taken to minimize the potential harmful effects. Originated by

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<sup>174</sup> McCullough, L.B., & Chervenak, F.A. (1994). Ethics in Obstetrics and Gynecology. New York: Oxford University Press, Inc., p. 47.

<sup>175</sup> McCullough, L.B., & Chervenak, F.A. (1994). Ethics in Obstetrics and Gynecology. New York: Oxford University Press, Inc., p. 37.

<sup>176</sup> McCullough, L.B., & Chervenak, F.A. (1994). Ethics in Obstetrics and Gynecology. New York: Oxford University Press, Inc., p. 39.

St. Thomas Aquinas in his deliberations about the morality of killing in self-defense, the double effect principle is applied in law, medicine, research, and the military to evaluate the ethics of actions with good intentions but adverse consequences.<sup>177</sup> Complicating the matter further, whether an outcome is a benefit (or a harm) can be judged differently by different people or by the same person in different contexts. Pregnancy itself is an example of such a dependent outcome – a joyfully anticipated occurrence at some times, a burden or even a danger to health and well-being in other people, contexts, or times. This lack of objective yardstick with which to assess the morality of any decision further necessitates fully informed consent and respect for autonomy.

In research, the principles of beneficence, nonmaleficence, and the double effect are operationalized in study design, methodology, and protocol development that minimize risks to the study participants. An Institutional Review Board (IRB), also called an independent ethics committee or an ethical review board, is responsible for objectively evaluating each study for its adherence to these principles, to prospectively assess the study's risks and benefits, and to assure potential harms to participants have been minimized. In the U.S., an IRB review is required by the FDA and the Office for Human Research Protection for any research that receives support either directly or indirectly from the Department of Health and Human Services.<sup>178</sup> IRBs are guided by The Common Rule (the common name for Subpart A, Part 46: Protection of Human Subjects, of Title 45: Public Welfare, in the Code of Federal Regulations (46 CFR 45) which contains the basic policy for protection of human research

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<sup>177</sup> McIntyre, A. (Fall, 2009). Doctrine of Double Effect, *The Stanford Encyclopedia of Philosophy*, Zalta, E.N. (Ed). Retrieved from <http://plato.stanford.edu/archives/fall2009/entries/double-effect/>

<sup>178</sup> Wikipedia contributors. (n.d.). Institutional Review Board. In *Wikipedia, The Free Encyclopedia*. Retrieved April 26, 2011 from [http://en.wikipedia.org/wiki/Institutional\\_review\\_board](http://en.wikipedia.org/wiki/Institutional_review_board).

subjects) and the international guidance documents that address human subjects research (e.g., the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, and CIOMS guidelines.)<sup>179</sup>

### c. The Principle of Justice

Justice was the "guiding ethical principle for the IOM committee" in their evaluation of the inclusion of women in clinical research.<sup>180</sup> The Belmont Report discusses the principle of justice in the research setting as requiring an "equitable distribution of the burdens and benefits of research."<sup>181</sup> Researchers must not include without good reason eligible candidates who may be harmed by participation, i.e. vulnerable persons. Nor can researchers "exclude without good reason eligible candidates who may benefit from participation."<sup>182</sup> When pregnant women do not have access to clinical research studies, they are denied the possibility of having the potential for benefit that is available to non-pregnant women - this violates the principle of justice.<sup>183</sup>

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<sup>179</sup>Miller, F.G. & Wertheimer, A. (2007). Facing up to paternalism in research ethics. *Hastings Center Report*, 37(3), 24-34.

<sup>180</sup>Rothenberg, K. (1996). The Institute of Medicine's report on women and health research: Implications for IRBs and the research community. *IRB: A Review of Human Subjects Research*, 18(2), 1-3.

<sup>181</sup>Levine, R.J. (1997). Ethics and Regulation of Clinical Research. New Haven, CT: Yale University Press, pp. 67-93. In Weijer, C., Dickens, B., & Meslin, E.M. (1997). Bioethics for clinicians: 10. Research ethics. *Canadian Medical Association Journal*, 156(8), 1153-1157, p. 1154.

<sup>182</sup>Levine, R.J. (1997). Ethics and Regulation of Clinical Research. New Haven, CT: Yale University Press, pp. 67-93. In Weijer, C., Dickens, B., & Meslin, E.M. (1997). Bioethics for clinicians: 10. Research ethics. *Canadian Medical Association Journal*, 156(8), 1153-1157, p. 1154.

<sup>183</sup>Kass, N.E., Taylor, H.A., & King, P.A. (1996). Harms of excluding pregnant women from clinical research: The case of HIV-infected pregnant women. *Journal of Law, Medicine & Ethics*, 24:36-46, p. 37.

Many individuals have been excluded from research as a means to protect them from being unfairly burdened by the potential harms of research; some are categorized in federal guidelines as “vulnerable.” Yet Levine et al. warn that the "concept of vulnerability stereotypes whole categories of individuals," including pregnant women, as being less than capable of making reasoned decisions.<sup>184</sup> The label itself may lead to injustice because it results in the exclusion of people who indeed have robust decisional capability from the opportunity to exercise that capacity in deciding whether their participation in research is in their best interests. Justice, state Lyerly et al., "calls into question the de facto summary exclusion of pregnant women in research without justification."<sup>185</sup>

#### d. Consequentialism

The question of inclusion/exclusion is at the basis of this study. In addition to Principlism, another "action-based" approach to ethics that addresses this issue is Consequentialism. This theory holds that the moral status of an action is determined by the goodness or badness of its outcomes. The Declaration of Helsinki, in some estimates the most influential document governing research world wide,<sup>186</sup> includes, in addition to autonomy, beneficence, and justice, an additional moral requirement for ethical research

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<sup>184</sup> Levine, C., Faden, R., Grady, C., Hammerschmidt, D., Eckenwiler, L., & Sugaman, J. (2004). The limitations of "vulnerability" as a protection for human research participants. *The American Journal of Bioethics*, 4(3), 44-49, p. 47.

<sup>185</sup> Lyerly, A.D., Little, M.O., & Faden, R.R. (2011). Reframing the Framework: Toward fair inclusion of pregnant women as participants in research. *The American Journal of Bioethics*, 11(5), 50-52, p. 51.

<sup>186</sup> Reich, W.T. (Ed). (1995). Declaration of Helsinki. *Encyclopedia of Bioethics*, revised ed. New York: Simon & Schuster MacMillan, p. 2765-7. In Weijer, C., Dickens, B., & Meslin, E.M. (1997). Bioethics for clinicians: 10. Research ethics. *Canadian Medical Association Journal*, 156(8), 1153-1157, p. 1155.

conduct: that patients' participation in research should not put them at a disadvantage with respect to medical care. I would argue that this requirement includes and requires its converse: that patients' *exclusion* from research should not put them at a disadvantage with respect to medical care. Stakeholders argue that the exclusion of pregnant women from medical research puts them decidedly at such a disadvantage. States Lisa Eckenwiler in a paper entitled, "Hopes for Helsinki: Reconsidering vulnerability,"...in this contemporary era of research, it is essential that codes of ethics move beyond merely protectionist thinking. Fair access to research participation should be addressed more explicitly."<sup>187</sup>

Eckenweiler takes the access issue a step further and thinks we should "...extend the scope of responsibility for ethical research to industry leaders, elected officials, and research funders, because they too play a role in ensuring that research endeavours do not create or perpetuate vulnerabilities, particularly inequalities in health or relations of power."<sup>188</sup> Inequalities of power are further addressed by the feminist theories that developed in the mid-20<sup>th</sup> Century.

## 2. Feminist Ethical Theory

The modern feminist approaches to ethical analysis arose in the 1970s in response to dissatisfaction with "moral" justifications of the status quo.<sup>189</sup> Traditional ethics were

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<sup>187</sup> Eckenwiler, L.A., Ells, C., Feinholz, D., & Schoenfeld, T. (2008). Hopes for Helsinki: Reconsidering vulnerability. *Journal of Medical Ethics*, 34(10), 765-766, p. 765.

<sup>188</sup> Eckenwiler, L.A., Ells, C., Feinholz, D., & Schoenfeld, T. (2008). Hopes for Helsinki: Reconsidering vulnerability. *Journal of Medical Ethics*, 34(10), 765-766, p. 765.

<sup>189</sup> Carter, L. (2002). Major ethical theories. Retrieved March 3, 2011 from University of Queensland Office of Public Policy and Ethics Web site: <http://www.uq.edu/au/oppe>

criticized for promoting culturally masculine traits like "independence, autonomy, intellect, will, hierarchy, domination, culture, wariness, war, and death" while dismissing culturally feminine traits like "interdependence, community, emotion, sharing, absence of hierarchy, connection, nature, trust, peace, and life."<sup>190</sup> Traditional ethics was also said to favor "'male' ways of moral reasoning that emphasize rules, rights, universality, and impartiality over 'female' ways of moral reasoning the emphasize relationships, responsibilities, particularity, and partiality."<sup>191</sup> Feminist perspectives sought to promote the importance of subjective experience in moral reasoning.

Feminist ethics is often linked with the 'ethic of care.' A term coined by moral psychologist Carol Gilligan, the ethic of care highlights certain salient moral considerations (context, particularity, relationships) that have not received due attention from traditional moral theories. But the ethic of care is only one of many feminist approaches. Others include liberal, radical, Marxist/socialist, multicultural, and ecological ethics where the emphasis is on questions of internal and external power, domination and subordination. Existentialist, postmodern and Third-Wave approaches focus on the psychological consequences of social status. These feminist approaches seek to identify and address the ways in which gender, class, and culture affect moral decision-making.

The feminist ethic of care aims primarily to identify and improve women's conditions – and, by extension, to improve circumstances for other vulnerable people like children,

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<sup>190</sup>Jaggar, A.M. (n.d.). Feminist ethics. In Becker, L. & Becker, C. (Eds). *Encyclopedia of Ethics*. New York: Garland Press, p. 363-4. In *Stanford Encyclopedia of Philosophy*. Retrieved from <http://plato.stanford.edu/entries/feminism-ethics/#2>

<sup>191</sup>Jaggar, A.M. (n.d.). Feminist ethics. In Becker, L. & Becker, C. (Eds). *Encyclopedia of Ethics*. New York: Garland Press, p. 363-4. In *Stanford Encyclopedia of Philosophy*. Retrieved from <http://plato.stanford.edu/entries/feminism-ethics/#2>



elderly, and minorities.<sup>192</sup> Its tenets include loving, caring, empathy, sensitivity and an emphasis on relationships and responsibilities. As the topic of this research study is the pregnant woman's relationships and responsibilities within the research community, with her health care provider and, most importantly, with her fetus, the care-oriented approach is, in my mind, extremely relevant. The feminist ethic of care is consistent with, but expands, the principlist ethic of beneficence.

The emphasis on relationships and responsibilities is in contrast to the individualistic approach in traditional ethics which are concerned with the rights of the individual. Carol Gilligan described moral development as growth from the individualistic perspective of the infant and child, to the growing realization of the person in relation to others, and finally to the mature person who can balance her individual needs with the needs of others.<sup>193</sup> This moral maturity results in an acceptance of responsibility for oneself and for the effect of one's actions on others.

In relation to this study, one might see the inclusion/exclusion question about pregnant women in clinical research from a traditional (i.e., male) perspective: avoiding harm by applying a rule (de jure or de facto) to all clinical studies: no pregnant women (or women capable of becoming pregnant) in clinical trials, period. But Gilligan, citing Piaget's findings, found that the female perspective encompassed "a greater tolerance, a greater tendency toward innovation in solving conflicts, a greater willingness to make exceptions to rules, and

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<sup>192</sup>Jaggar, A.M. (n.d.). Feminist ethics. In Becker, L. & Becker, C. (Eds). Encyclopedia of Ethics. New York: Garland Press, p. 363-4. In *Stanford Encyclopedia of Philosophy*. Retrieved from <http://plato.stanford.edu/entries/feminism-ethics/#2>

<sup>193</sup>Burton, B.K. & Dunn, C.P. (1996). Feminist ethics as moral grounding for stakeholder theory. *Business Ethics Quarterly*, 6(2), 133-147.

a lesser concern with legal elaboration."<sup>194</sup> Thus, including the feminist ethic to the framework of this study not only promotes the perspective of the primary subject of concern (women), but broadens the discussion and opens the deliberation to innovation, flexibility, context, and particularity.

Rather than being dichotomous or contradictory, however, can we find parallels between the traditionalist and the feminist approaches? We discussed the principles of autonomy, beneficence, and justice as being the foundation of medical and research ethics both in theory (see the ethical codes) and in clinical and research practice. Are these principles compatible with feminist theory and practice?

Paternalism – "overriding the [competent person's] wishes or intentional actions [even if] for beneficent reasons"<sup>195</sup> - is an "offense to the autonomy of [competent] persons"<sup>196</sup> and would be unacceptable to the principlist's "respect for persons" and to the "ethic of care." Beneficent, care-oriented practitioners would embody respect for persons by sharing their knowledge, their experience, their preferences and the rationale for those preferences, with the woman/patient/potential research subject. They would encourage the woman to include her own unique subjective experiences, preferences, and knowledge interpretations in her deliberations. Perspective sharing from the woman's own "experts" of choice – her personal supporters (e.g., the father of the fetus, family members, friends) – would also be

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<sup>194</sup>Gilligan, C. (1987). Moral orientation and moral development. In Kittay, E.F. & Meyers, D.T. (Eds.), Women and Moral Theory. Lanham, MD: Rowman & Littlefield Publishers, Inc.

<sup>195</sup>McCullough, L.B., & Chervenak, F.A. (1994). Ethics in Obstetrics and Gynecology. New York: Oxford University Press, Inc., p. 268.

<sup>196</sup>McCullough, L.B., & Chervenak, F.A. (1994). Ethics in Obstetrics and Gynecology. New York: Oxford University Press, Inc., p. 45.

encouraged. The formulation of a decision in this manner is dense with relationships and responsibilities. Thus, the care-oriented practitioner, in respectful relationship with her patient, enables her autonomy.<sup>197,198</sup> This is fully informed consent.

Parallels exist between the ethic of care and the principle of beneficence because both seek to induce beneficial outcomes and refrain from causing harm. Nel Noddings suggests that the caring behavior we naturally exhibit as children, helping others simply because we want to help them, develops into ethical caring as we grow to live in the complex external world.<sup>199</sup> She further states that "having a robust sense of social justice is predicated on the lessons learned in the private sphere." Thus there are parallels between beneficence and justice and the ethic of care perspective as well. This suggests that both the principle-based approach and the care-oriented approach can, and do, co-exist. Carol Gilligan states that all human relationships can be viewed from the justice perspective in terms of equality ("don't act unfairly towards others") and from the ethic of care perspective in terms of attachment ("don't turn away from someone in need").<sup>200</sup> Utilizing both perspectives buttresses the argument for inclusiveness. Gilligan challenges both men and women to "speak the moral language of justice and rights as fluently as the moral language of care and responsibility."<sup>201</sup>

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<sup>197</sup>Kukla, R. (2005). Conscientious autonomy: Displacing decisions in health care. *Hastings Center Report*, 35(2), 34-44.

<sup>198</sup>Kukla, R. (2007). How do patients know? *Hastings Center Report*, 37(5), 27-35.

<sup>199</sup>Zalta, E.N. (Ed). (2009). Feminist Ethics. In *The Stanford Encyclopedia of Philosophy*. Retrieved April 18, 2011 from <http://plato.stanford.edu/entries/feminism-ethics/#2>, citing Noddings N. (1984). *Caring: A Feminine Approach to Ethics and Moral Education*. Berkeley: University of California Press.

<sup>200</sup>Gilligan, C. (1987). Moral orientation and moral development. In Kittay, E.F. & Meyers, D.T. (Eds.), Women and Moral Theory. Lanham, MD: Rowman & Littlefield Publishers, Inc.

<sup>201</sup>Gilligan, C. (1982). In a Different Voice: Psychological Development and Women's Development. Cambridge, MA: Harvard University Press in Feminist Ethics. (n.d.). In *Stanford Encyclopedia of Philosophy*. Retrieved on April 18, 2011 from <http://plato.stanford.edu/entries/feminism-ethics/#2>

In conjunction with the principle-based ethical framework that is commonly evoked by medical and research practitioners, the feminist ethic of care perspective is relevant to this research effort. Caring is central to women's experience – not just pregnant women's experience. Women may be never pregnant, pre-pregnant, pregnant, or post-pregnant at different times in their lives. And many women and men care for and about pregnant women – be they their health care providers, their significant others, their parents, their children, or their friends. The safety and effectiveness of medical intervention in clinically compromised pregnancies impacts, and is of concern to, many people on a fundamentally sensitive loving, caring basis.

Alison Jaggar<sup>202</sup> describes the outcomes that all approaches to feminist ethics seek to achieve:

1. to articulate moral critiques of actions and practices that perpetuate women's subordination
2. to prescribe morally justifiable ways of resisting such actions and practices
3. to envision morally desirable alternatives for such actions and practices
4. to take women's moral experience seriously, though not uncritically

These aims parallel the aims of this research study: by articulating the views of the U.S. pharmaceutical industry, to find common purpose and mutually beneficial approaches to including pregnant women, who have historically been excluded, in clinical research studies.

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<sup>202</sup>Jaggar, A.M. (n.d.). Feminist ethics. In Becker, L. & Becker, C. (Eds). *Encyclopedia of Ethics*. New York: Garland Press, p. 363-4. In *Stanford Encyclopedia of Philosophy*. Retrieved from <http://plato.stanford.edu/entries/feminism-ethics/#2>

### 3. Business Ethics

The discovery and development of pharmaceutical agents is a complex and costly endeavor. Knowledge of chemistry, pharmacology, biochemistry, microbiology, genomics, toxicology, and clinical medicine are required. Once a potentially viable product reaches the end of the labyrinth of development, the product then needs manufacture, packaging, production, distribution, promotion, ongoing monitoring, fiduciary and legal support. The need for all of these highly sophisticated and closely regulated functions requires a complex interdisciplinary organization – the pharmaceutical industry.

In the pharmaceutical industry, medical practitioners work collaboratively with research scientists on the design, conduct, and evaluation of clinical studies. The goal to obtain objective and definitive scientific data that support the use of preventative or curative therapies by people in need satisfies both the clinical and the research agenda. But there is a third agent whose needs are also present – the corporate agenda.

What are the generally acceptable ethical principles for the corporation? I had a hard time finding their definition in the literature. Many papers analyzing ethical failures were available but I did not find a generally accepted ethical framework for business. I did find a description of three potential vantage points from which business ethics could be derived that were instructive.<sup>203</sup> They are:

- 1) Ethics derived from the profit motive – including ‘good ethics result in good business’ (i.e., the best interests of a business are served by establishing a trusting relationship with the public [resulting in increased product loyalty, and decreased liability claims] and

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<sup>203</sup>Fieser, J. Business ethics. (n.d.) Retrieved April 16, 2011 from <http://www.utm.edu/staff/jfieser/vita/research/Busbook.htm>

employees [resulting in good morale and productivity]) and its reverse, ‘good business results in good ethics’ (i.e., the demand for moral behavior from customers and employees will result in proper behavior from companies). Businesses that meet these demands will survive and prosper.

2) Ethics derived from the legal system – businesses will do the right thing as prescribed by the law; any obligation beyond the law is optional.

3) Ethics derived from general moral obligations -

- *Harm principle*: businesses should avoid causing unwarranted harm.
- *Fairness principle*: business should be fair in all of their practices.
- *Human rights principle*: businesses should respect human rights.
- *Autonomy principle*: businesses should not infringe on the rationally reflective choices of people.
- *Veracity principle*: businesses should not be deceptive in their practices.
- *Stakeholder principle*: businesses should consider all stakeholders' interests that are affected by a business practice.

Most companies utilize a combination of these three approaches to guide decision-making and the pharmaceutical companies would be no exception. But medical research is fundamental to this industry's ability to discover, produce, and maintain its products.

Therefore, the ethical framework for medical research must be compatible with the ethical framework of the business. The third approach, ethics derived from general moral obligations, is the most compatible with research ethics and the principle-based and feminist approaches described above. The Harm and Veracity principles correspond to Nonmaleficence, the Fairness principle to Justice, and the Autonomy and Human Rights principles to Respect for Persons.

One could propose that the Stakeholder principle corresponds to the consequentialist principle discussed above, i.e., the business practice of excluding pregnant women from

research studies may not be in women's best interests. On the other hand, including pregnant women in research studies may not be in the company's best interests.

The founders of Stakeholder theory, Freeman and Gilbert,<sup>204</sup> "view business as a connected set of relationships among stakeholders built [not upon the traditionalist] principles of competition and justice but [on] cooperation and caring."<sup>205</sup> Burton and Dunn<sup>206</sup> propose parallels between stakeholder and feminist theories as these both promote the centrality of relationships as the basis upon which knowledge is gained, options are considered, and decisions should be made. In individualistic rights-based organizational theory, the firm is in competition with other firms and seeks to further its own interests. Legal contracts replace trust-based relationships to protect the company in negotiations. In stakeholder theory, firms take a more cooperative stance, seeking decisions where all parties gain. This can only happen when the company makes the stakeholders interests explicit and considers the effects of the proposed decisions on all parties involved. Burton and Dunn believe that a rights-based view is inherently problematic when differences of opinion arise. If competing parties are trying to get their 'inherent rights' met - but no one's rights supersede another one's rights - a stalemate is reached. In Stakeholder theory, companies try to do the "right" thing. When differences of opinion arise, Burton and Dunn invoke the ethic of care and propose that the company should "care enough for the least advantaged stakeholders that

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<sup>204</sup>Freeman, R.E. & Gilbert, D.R. (1992). Business, ethics and society: A critical agenda. *Business & Society*, 31(1), 9-17.

<sup>205</sup>Burton, B.K. & Dunn, C.P. (1996). Feminist ethics as moral grounding for stakeholder theory. *Business Ethics Quarterly*, 6(2), 133-147.

<sup>206</sup>Burton, B.K. & Dunn, C.P. (1996). Feminist ethics as moral grounding for stakeholder theory. *Business Ethics Quarterly*, 6(2), 133-147.

they not be harmed." "A firm following this principle must perform a stakeholder analysis not merely to understand which stakeholders have power and which have a stake in the decision, but also to understand which stakeholders are most vulnerable to the action."<sup>207</sup> This combination of stakeholder theory and feminist ethics may inform this study's conceptual approach to interactions with pharmaceutical company and related organization representatives and to the proposal of procedural change within the industry.

There are many examples of pharmaceutical company philanthropic activities contributing to the public health needs of populations at risk. Some feel that these "good deeds have not been given the credit and recognition they deserve."<sup>208</sup> They have been overshadowed by stories of unlawful marketing practices, unfair pricing practices, suppression of safety and efficacy data, and manipulative business practices.<sup>209</sup> The challenge before the pharmaceutical industry is to find the portfolio of products that maintains commercial success (ensuring profitability and shareholder value) while addressing a range of unmet medical needs (fulfilling social and political responsibilities). To do the right thing and to overcome negative public perception based on past shortcomings, the successful company must maintain corporate integrity by strictly adhering to ethical research and business practices.

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<sup>207</sup>Burton, B.K. & Dunn, C.P. (1996). Feminist ethics as moral grounding for stakeholder theory. *Business Ethics Quarterly*, 6(2),133-147, p. 144.

<sup>208</sup>Koski, E.G. (2005). Renegotiating the grand bargain: Balancing prices, profits, peoples, and principles. In Santoro, M.A., & Gorrie, T.M. *Ethics and the Pharmaceutical Industry*. New York, NY: Cambridge University Press, 2005, p. 395.

<sup>209</sup>Koski, E.G. (2005). Renegotiating the grand bargain: Balancing prices, profits, peoples, and principles. In Santoro, M.A., & Gorrie, T.M. *Ethics and the Pharmaceutical Industry*. New York, NY: Cambridge University Press, 2005, p. 394.



## **B. Special Considerations for Pregnancy/Maternal-fetal Ethics**

Vulnerable subjects are those people whose rights need the most protection. These groups, according to federal regulations, include children, incapable adults, prisoners, and pregnant women. Lupton states that, "While children, incapable adults, and prisoners are vulnerable because they lack freedom or autonomy, what distinguishes pregnant women from the rest of the population is the prospect of causing harm to vulnerable 'future people' (their unborn children)."<sup>210</sup> According to him, it is the fetus who is vulnerable to having its consent given by a proxy since it is incapable of giving it itself. Do we suspect that a pregnant woman might disregard or minimize the risk to her fetus when a study might provide benefit to her? In the first place, benefit to the health of the pregnant woman usually provides benefit to the fetus as well. Secondly, it is hard to imagine who would care more about protecting and enhancing the health of the fetus than the expectant mother.

Or is the gravid woman vulnerable in her own right? A woman does not lose reasoning capacity when she becomes pregnant. Yet her concern for her developing fetus might influence her decision-making. Might a pregnant woman accept a higher risk to herself in the interests of aiding her fetus? Might it be a risk that would be unacceptable to a non-pregnant subject? Is this what the FDA research guidelines attempt to address by requiring, to the extent possible, that the father of the fetus also provide consent in the case of a therapeutic intervention that is beneficial only to the fetus? Is it to protect the woman from

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<sup>210</sup>Lupton, M.G.F., & Williams, D.J. (2004). The ethics of research in pregnant women: Is maternal consent sufficient? *British Journal of Obstetrics and Gynecology*, 111, 1307-1312, p. 1308.

herself (her altruism, her love, her compassion)? Or is the regulatory agency implying that the woman is less than capable of making the decision herself?

Is the pregnant research subject more or equally prone to "the therapeutic misconception"<sup>211</sup> – "the tendency of patient-subjects to mistakenly assume that research interventions are designed to benefit them"<sup>212</sup> – and thus be more willing to consent to participate in a study? Or are they more prone, as research has shown, to overestimate the risk of all exposures that inadvertently or purposefully occur during the course of a pregnancy<sup>213,214</sup> - and thus be less likely to participate in research?

Is the classification of the pregnant woman as 'vulnerable' to protect her interests or to protect the fetus' interests? Is it the pregnant woman who is vulnerable or should we say that children, the incompetent, prisoners, and *fetuses* are vulnerable groups?

I find that I am not alone in my perplexity about the characterization of pregnant women as a vulnerable group. In a paper entitled "The two dimensions of subject vulnerability"<sup>215</sup> in the *Journal of Clinical Research Best Practices*, the author, Norman Goldfarb, depicts vulnerable groups on a graph. On the x-axis is the Ability to Give Informed

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<sup>211</sup> Appelbaum, P.S., Roth, L.H., Lidz, C.W., Benson, P., & Winslade, W. (1987). False hopes and best data: Consent to research and the therapeutic misconception. *Hastings Center Report*, 17(2), 20-24.

<sup>212</sup> Miller, F.G. & Wertheimer, A. (2007). Facing up to paternalism in research ethics. *Hastings Center Report*, 37(3), 24-34, p. 29.

<sup>213</sup> Pole, M., Einarson, A., Paireudeau, N., Einarson, T., & Koren, G. (2000). Drug labeling and risk perceptions of teratogenicity: A survey of pregnant Canadian women and their health professionals. *Journal of Clinical Pharmacology*, 40, 573-77.

<sup>214</sup> Koren, G., & Levichek, Z. (2002). The teratogenicity of drugs for nausea and vomiting of pregnancy: Perceived versus true risk. *American Journal of Obstetrics & Gynecology*, 186(5), S248-52.

<sup>215</sup> Goldfarb, N. (2006). The two dimensions of subject vulnerability. *Journal of Clinical Research Best Practices*, 2(8), 1-3, p. 2.

Consent and on the y-axis is Resistance to Undue Influence and Coercion with the identified groups ranging in placement on scales from low to high on each axis. The 20 vulnerable groups depicted include, among others, all of the vulnerable groups defined in the Code of Federal Regulation – except pregnant women. It seems Mr. Goldfarb did not know where to place pregnant women either. He did, however, include "Unborn" as a vulnerable group, low on the x-axis and high on the y-axis. So perhaps he agrees with Lupton and interprets the regulations to mean that it is the fetus and not the pregnant woman who is vulnerable.

Respect for persons requires that the choices of *autonomous* individuals be respected *and* that people who are incapable of making their own choices be protected (italics mine).<sup>216</sup> This presents a conundrum for the investigator with a pregnant subject. On the one hand, the pregnant woman and the fetus are not autonomous in the limited sense of being independent. The fetus is wholly dependent on its 'host.' Therefore, the mother's 'choice' should be sufficient consent. However, the fetus is an entity who is incapable of making its own choice and whose interests, like those of children, deserve extra layers of protection.

Who speaks for the fetus? According to FDA guidelines, it is sometimes the mother and sometimes the mother and the father. According to American jurisprudence, it is sometimes the government. There are cases of government ruling with health care providers to force pregnant women to have C-sections for the "good of the fetus." In one notorious case, neither the mother nor the infant survived. In that case, the court subsequently ruled that

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<sup>216</sup>Weijer, C., Dickens, B., & Meslin, E.M. Bioethics for clinicians: Research ethics. *Canadian Medical Association Journal*, 156(8), 1153-1157.

"neither fetal rights nor state interests on behalf of the fetus supersede women's rights as ultimate medical decision maker."<sup>217</sup>

The ACOG Committee on Ethics has taken a position on the balancing of the mother's and the fetus' interests. The Committee Opinion is that "efforts to use the legal system specifically to protect the fetus by constraining women's decision making or punishing them for their behavior erode a woman's basic rights to privacy and bodily integrity are neither legally nor morally justified."<sup>218</sup> They recognize that the intertwined interests of the maternal-fetal unit usually "converge rather than diverge"<sup>219</sup> but, in either case, it is the responsibility of the woman to consent or refuse to participate in medical therapy or in clinical research.

### **C. Conclusion: Application of the Ethical Framework**

I have reviewed the ethical principles and theories most frequently invoked when discussing clinical research, medical practice, women's interests, and business practices. I conclude that an ethical framework for evaluating perspectives about the inclusion of pregnant women in clinical research should be based upon the ethical principles of:

- 1) Autonomy, or Respect for Persons, including the avoidance of paternalism

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<sup>217</sup> Harris, L.H. (2003). The status of pregnant women and fetuses in U.S. criminal law. *Journal of the American Medical Association*, 289(13),1697-1699, p. 1698.

<sup>218</sup> American College of Obstetricians and Gynecologists. (2005) Maternal decision making, ethics, and the law. ACOG Committee Opinion No. 321. *Obstetrics and Gynecology*,106, 1127-37, p. 1135.

<sup>219</sup> American College of Obstetricians and Gynecologists. (2005) Maternal decision making, ethics, and the law. ACOG Committee Opinion No. 321. *Obstetrics and Gynecology*,106, 1127-37, p. 1135.

- 2) Beneficence, Nonmaleficence, and the Double Principle, including the avoidance of causing disadvantage
- 3) Justice
- 4) Care
- 5) Stakeholder Considerations, including as stakeholders both the pregnant woman and her caregivers and the drug company and its researchers

This ethical framework helped in the design of the study and the construction of the interview guide. The ethical issues that this study raises are best explored via dialogue – hence the qualitative design and the interview approach. It informed the construction of the interview guide by helping to identify the relative importance of potential questions and what terminology and concepts would be most readily understood by the interviewees.

This ethical framework will aid the application of ethical principles to potential solutions proposed to address the dilemma of whether or not to include pregnant women in research studies. As with most ethically-laden situations, no completely "right" or "wrong" solutions will likely be obvious. No one solution will be correct in every situation. Just as it is would be unethical to require the inclusion of pregnant women in all clinical trials, it is unlikely that the exclusion of pregnant women from all clinical trials would be ethically permissible either. Having an ethical framework to inform deliberations will facilitate the formulation of solutions and exceptions to those solutions upon which stakeholders can agree. Table 3.1 illustrates a potential application of this ethical framework to the potential solutions proposed by various stakeholders to address the inclusion of pregnant women in clinical research.

This framework provides a structure and a common basis upon which to justify conclusions. In this arena, where both the pros and cons of the inclusion of pregnant women in research can be argued on ethical merits (see Chapter 2), a framework in the accepted language of medical, research, feminist, and business theory, will assist stakeholders in the understanding and consideration of options.

### **Table 3.1 Application of an ethical framework to this study**<sup>\*220</sup>

Each rationale proposed to address pregnant women's inclusion in, or exclusion from participation in clinical research can be evaluated using the following ethical analysis:

#### **Autonomy/Respect:**

Does this rationale/solution impinge on anyone's personal autonomy?  
Do all relevant parties consent to this rationale/solution? If not, what are the objections?  
Are all opinions acknowledged and respected?

#### **Beneficence:**

Who benefits from this rationale/solution and in what way?  
Does the rationale/solution use the best of our current knowledge?  
Does the rationale/solution favor the balance of benefit over risk?

#### **Non-maleficence:**

Who may be harmed by this rationale or the implementation of this solution?  
How have the potential harms been minimized?  
Are risks communicated in a truthful, complete, and open manner?

#### **Justice:**

Is the rationale/proposed solution equitable to all stakeholders?  
Can it be made to be more equitable?  
Are the benefits and the burdens fairly distributed among stakeholders?

#### **The Ethic of Care:**

Whose needs are being met by this solution?  
Does the rationale/solution promote cooperation among stakeholders?  
Are relationships identified and maintained or promoted by the action?

#### **Stakeholders:**

Have all parties involved in this rationale/solution been identified?  
What parties are impacted by this rationale/solution and in what way?  
Are all stakeholders' concerns respected and addressed?

\*Adapted from Beauchamp and Childress

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<sup>220</sup> Adapted from Beauchamp, T. & Childress, J. (2001). *Principles of Biomedical Ethics* (5<sup>th</sup> ed.) Oxford: Oxford University Press. In The Office of Public Policy and Ethics (2002), A primer to ethical analysis. Retrieved March 6, 2011 from The University of Queensland web site: <http://www.uq.edu.au/oppe>

## **Chapter 4**

### **Study Design and Methods**

#### **A. Overall Study Purpose**

There is a dearth of information from the U.S. pharmaceutical industry regarding the inclusion of pregnant women in clinical research studies. The extent of pregnant women's exclusion has not been quantified, nor has the industry's rationale for their exclusion been articulated. The purpose of this concurrent mixed methods study was to better understand the U.S. pharmaceutical industry's practices and perspectives about the inclusion of pregnant women in clinical research.

The qualitative and quantitative methodologies were performed concurrently from October 2011 through January 2012. The quantitative portion sought to confirm and quantify the current practice of excluding pregnant women from clinical studies. It provided a view into current practice. The qualitative interviews did not rely upon this information. The qualitative study sought to explore the rationale behind current practice and elicit potential barriers to, and opportunities for, change. Triangulating information from both portions of the overall study provided a broad picture of current practice and resulted in proposals for a path forward.



## **B. Quantitative Study Design and Methods**

### **1. Quantitative Study Purpose**

This study quantified the practice of excluding pregnant women by reviewing the inclusion/exclusion criteria of all U.S. based, open Phase IV interventional drug studies with adult female participants sponsored by industry currently posted on ClinicalTrials.gov.

As the responsible entity for the cost, conduct, and outcome of clinical trials, pharmaceutical companies determine whether pregnant women will be included in or excluded from enrollment in each study.

Clinical trials have traditionally excluded pregnant women to protect their fetuses from exposure to experimental medications with unknown safety risks. But this practice has contributed to a lack of information about how to treat medical conditions that can complicate pregnancies. This does not mean that all studies should include pregnant women. Reasons for their exclusion should be considered prior to study initiation. For example, it would be reasonable to exclude pregnant women from drug studies for which therapeutic benefit is undetermined.

This study quantified the frequency with which pregnant women are excluded from current Phase IV clinical trials evaluating treatments for diseases or conditions that could affect a pregnancy. Phase IV trials are conducted using drugs that have already received regulatory approval and are currently marketed in the U.S. They evaluate issues about safety, concomitant medication interactions, or use in populations other than those for which the drug was initially approved. Almost any type of clinical study may be conducted in the post-

marketing environment.<sup>221</sup> Because these drugs have been studied in clinical trials, approved by FDA, and are on the market, more safety and efficacy information is available and the benefit-risk relationship is better established. These studies are, therefore, some of the most appropriate studies in which pregnant women could participate. The exclusion of pregnant women from these studies served as a proxy for the practice of exclusion of pregnant women from all phases of drug trials.

For drugs in development, animal studies are performed to predict the potential for toxicity and teratogenicity. FDA weighs the pregnancy risk information during the process of approval and a pregnancy risk category (see below) is added to the products' label. This risk category is available for all drugs being studied in Phase IV trials.

## **2. Quantitative Question**

What proportion of open U.S. pharmaceutical industry-sponsored Phase IV clinical trials currently enrolling women include pregnancy in their exclusion criteria?

## **3. Quantitative Data source**

Inclusion/exclusion criteria of all U.S.-based, industry-sponsored open Phase IV interventional drug studies enrolling women of childbearing potential currently posted on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

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<sup>221</sup>Spilker, B. (1996). Guide to Clinical Trials. Philadelphia: Lippincott Raven, p. 44.

ClinicalTrials.gov provides public access to the list of federally and privately supported clinical trials currently being conducted to investigate experimental treatment for a wide range of diseases and conditions. The website was developed to provide public information about current clinical trials so that individuals with serious diseases and conditions might access experimental treatments and volunteer to participate in the studies. It also provides a resource to access the basic results of completed clinical trials.<sup>222</sup>

According to its website, ClinicalTrials.gov currently contains 102,470 trials sponsored by the National Institutes of Health, other federal agencies, and private industry. Studies listed in the database are conducted in all 50 States and in 174 countries. The NIH, through its National Library of Medicine, has developed this site in collaboration with the FDA, as a result of the FDA Modernization Act, which was passed into law in November 1997.”<sup>223</sup>

This study was limited to the review of open (i.e., currently enrolling) U.S.-based Phase IV (i.e. post-marketing) interventional studies (i.e., “trials [to] determine whether experimental treatments or new ways of using known therapies are safe and effective under controlled environments” as opposed to observational trials that “address health issues in large groups of people or populations in natural settings”)<sup>224</sup> that include adult (i.e. age 18 to 65) female participants and are sponsored by a pharmaceutical company. To be included, the study must have been evaluating treatment of conditions that may be experienced by, but are

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<sup>222</sup>ClinicalTrials.gov. Protocol Registration System. (2012). Retrieved on Feb. 6, 2012 from <http://prsinfo.clinicaltrials.gov/fdaaa.html>

<sup>223</sup>National Institutes of Health. (2011). About ClinicalTrials.gov. Retrieved Feb. 6, 2011 from <http://clinicaltrials.gov/ct2/info/about>

<sup>224</sup>National Institutes of Health. (2011). About ClinicalTrials.gov. Retrieved Feb. 6, 2011 from <http://clinicaltrials.gov/ct2/info/about>

not limited to, pregnant women and they must not have involved the use of a medication that is in the FDA pregnancy categories D or X – those thought to be potentially teratogenic. See further description and other restrictions in Limitations, below.

#### **4. Quantitative Methodology**

Analysis of the inclusion/exclusion criteria regarding pregnant women in U.S. clinical trial protocols as posted on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) resulted in a listing of current studies by the following variables and characteristics:

1. Search criteria:
  - a. Open studies
  - b. Interventional studies
  - c. Included male and female or only female subjects
  - d. Adult age group (18-65)
  - e. Pharmaceutical company-sponsored
  - f. Concern conditions that may be experienced by, but are not limited to, pregnant women
2. Study Phase
  - a. Phase IV studies only (n = 348 as of August 1, 2011)
3. Variables from ClinicalTrials.gov included: Study ID#, Name of Study, Drugs, Sponsor, Condition, Estimated enrollment, Inclusion Criteria, and Exclusion Criteria, Contact Information, Description

4. Variables added included: Disqualification Reason, Pregnancy Category, No mention of pregnancy in inclusion or exclusion criteria, Contact Called Y/N, Result of Contact – Included/Excluded/Unknown, Notes

Clinical trials were excluded from the analysis if the age (e.g., postmenopausal), condition (e.g., amenorrhea), or drugs being tested (e.g., pregnancy risk category D or X) would preclude the enrollment of pregnant women. The FDA pregnancy category for all of the drugs identified for use in each study was identified by viewing the pregnancy section of their prescribing labels on PDR.net. (See Table 4.1 for a description of pregnancy categories.) Studies using drugs with FDA pregnancy category D or X were excluded.

**Table 4.1 FDA Pregnancy Risk Categories<sup>225</sup>**

Category	Description
A	<b>Controlled studies show no risk</b> -Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
B	<b>No evidence of risk in humans</b> -Adequate, well controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals, <b>or</b> In the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.
C	<b>Risk can not be ruled out</b> - Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk.
D	<b>Positive evidence of Risk</b> -Studies in humans, or investigational or post marketing data, have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life threatening situation or serious disease for which safer drugs cannot be used or are ineffective.

<sup>225</sup> American Pregnancy Association. (2006). FDA Drug Category Ratings. Retrieved on Aug. 2, 2011 from <http://www.americanpregnancy.org/pregnancyhealth/fdadrugratings.html>

X	<b>Contraindicated in Pregnancy-</b> Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient.
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## 5. Analysis Plan: Quantitative Study

### A. Descriptive statistical analysis of data included

1. Total number of studies included
2. Total number of studies disqualified
3. Range of enrollment numbers
4. Number of studies excluding pregnant women as noted in the inclusion criteria
5. Number of studies excluding pregnant women as noted in the exclusion criteria
6. Number of studies inclusion/exclusion criteria that did not mention pregnancy or require birth control
  - a. Number of these studies contacted
  - b. Result of contact – included pregnant women, excluded pregnant women, or remained unknown
7. Total number and proportion of studies that included pregnant women
8. Total number and proportion of studies that excluded pregnant women

## 6. Limitations of Quantitative Analysis

a. Delimitations – studies were limited to open U.S. Phase IV clinical trials sponsored by industry that enrolled women and were posted on ClinicalTrials.gov. ClinicalTrials.gov includes all U.S. clinical trials that are approved by FDA and sponsored by the pharmaceutical industry.

The study was limited to Phase IV trials because they are the most appropriate trials in which pregnant women can participate, as described above. In addition, Phase I, II, and III trials were excluded because the safety data of the unapproved drugs being evaluated are not available in the public domain. Therefore, I would have been unable to evaluate if it would be appropriate for pregnant women to be included in such studies.

b. Limitations – Some of the inclusion and exclusion criteria listed by the study sponsors on ClinicalTrials.gov may not have been fully inclusive and may not have mentioned pregnancy or pregnancy potential. It may not be accurate to assume that if pregnancy was not mentioned as an exclusion criterion then pregnant women were included as study subjects. In order to validate the initial findings from the website, any protocols that did not mention pregnancy or pregnancy prevention per se were contacted via a phone call or email to the study contact to attempt to verify if pregnant women had access to enrollment in the trial.

However, this still may not have addressed de facto exclusion, i.e. the "inadvertent" failure to recruit pregnant women (as opposed to exclusion de jure, i.e. the explicit exclusion of pregnant women in the protocol).<sup>226</sup> In other words, just because a study did not exclude pregnant women in the protocol, did not mean that pregnant women would be enrolled. This was a point of discussion for the studies that were contacted.

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<sup>226</sup>Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 370.

## **C. Qualitative Study Design and Methods**

### **1. Qualitative Study Purpose:**

Concurrently with compiling the quantitative data described above, this study sought to understand the perspectives of key opinion leaders in the pharmaceutical industry and related organizations, using qualitative key informant interviews to identify key themes regarding the rationale for exclusion and the opportunities for inclusion ones.

### **2. Qualitative Study Question**

What are the current perspectives of U.S. pharmaceutical industry representatives and those of related organizations about the inclusion of pregnant women in clinical research studies?

Key informant interviews provided data to explore why pharmaceutical companies may be limiting pregnant women's access to participation in clinical trials and how more inclusive practices may be adopted.

### **3. Qualitative Data Source**

Key Informant Interview data: semi-structured interviews with subject matter experts in the U.S. pharmaceutical industry, professional groups, and related organizations:

- a. Clinical researchers or other staff working in U.S. pharmaceutical companies (n=5) and biotech firms (n=3)
- b. Legal representatives from pharmaceutical companies (n=2) and PhRMA (n=1)



- c. Pharmaceutical Research and Manufacturers of America [PhRMA] representative (n=1)
- d. Independent Institutional Review Board members (n=3) who are contracted by industry to review their protocols
- e. Food and Drug Administration representative (n=1)

#### **4. Qualitative Methodology**

Key Informant Interviews - I identified key informants by using my past experience working on pregnancy registries within the pharmaceutical industry and the relationships I built with others working in this field. In qualitative research, participants who will best help the researcher address the study questions are purposefully selected (as opposed to the random selection used in quantitative research).<sup>227</sup> Some informants were known to me and others were recommended by them or by others (e.g., committee members)..

Potential participants were initially contacted by me either via email or by phone. I explained the purpose of the study and why I was requesting their participation. The qualitative methodology was described. I clarified that I was seeking their personal opinion (not that of their organization) because of their experience in clinical research in the pharmaceutical industry or related organizations. If they agreed to participate, I allowed them to suggest when and where they would prefer to be interviewed (i.e., during working hours or at another time).

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<sup>227</sup>Creswell, J.W. (2003). Research Design: Qualitative, Quantitative, and Mixed Methods Approaches, (2<sup>nd</sup> ed). Thousand Oaks, CA: Sage Publications, p.185.

One hour telephone interviews were scheduled with each participant in advance. A pre-designed interview protocol was constructed and included an introduction, background for the key informants, the key research questions, and probes to follow the research questions. The key research questions, a small number of open-ended interview questions intended to elicit views and opinions of the participants,<sup>228</sup> were utilized for consistency. The interview guide was provided to them 2 weeks in advance of the scheduled interview to allow the informants time to consider the issues or consult with others within their organization. (See Interview Guide, Appendix III.)

The interviews were tape-recorded with the participant's permission. Interview recordings were transcribed.

## **5. Qualitative analysis of key informant interview data**

The interview transcripts were systematically manually coded and evaluated to identify key themes and issues. Evaluation of the data proceeded from the general (overview, high-level ideas, impressions) to the specific (coding similar ideas, clustering similar ideas into topics, labeling topics as codes, applying codes to the texts, identifying coded segments of text that best describe the concepts).

Interpretation of the coded data: Codes were evaluated in categories such as expected themes (those that relate the findings to the historical information gathered from the literature), unexpected themes, and themes that relate to principles in the theoretical framework.

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<sup>228</sup>Creswell, J.W. (2003). Research Design: Qualitative, Quantitative, and Mixed Methods Approaches, (2<sup>nd</sup> ed). Thousand Oaks, CA: Sage Publications, p. 188.

Confidentiality of key informants' identities is strictly maintained. All informant data is presented anonymously with no reference to the informant's name. Interview recordings and transcripts are kept in a locked cabinet. Aside from the original documents, all subsequent documents are key-coded as to the identity of the informant. The Key code is held in a locked cabinet separate from the original documents.

Themes are identified by type of organization (pharmaceutical or biotech company), legal representative, PhRMA representative, IRB representative, or FDA representative. No names of individuals are identified.

Key themes were identified. Multiple perspectives about each theme are presented in the Results section (Chapter 6). Specific quotations related to the themes are highlighted. Relationships between themes are identified and explored.

These findings are interpreted and applied to the issues raised by the literature and by proponents of the rational inclusion of pregnant women in clinical trials. Where do the themes of industry and related organizations agree with and where do they diverge from themes identified in the literature and by proponents of the inclusion of pregnant women in clinical research trials? Are opportunities or barriers to change identified? Are there recommendations that can be promoted to inform discussion, policy, or practice about the inclusion of pregnant women in medical research? (See Chapter 6).

## **6. Limitations of Qualitative Data**

a. Delimitations – Key informants were limited to 16 participants in the U.S. organizations identified above. This does not include informants from all companies or

organizations that may potentially be knowledgeable about the subject matter. These participants may or may not represent the perspectives of other companies and organizations or a consensus on the subject.

b. Limitations – Telephone interviews were subject to limitations of not being in physical proximity to the participant. Visual clues such as body language and facial expressions were lost.

Some of the key informants were chosen by me (convenience sample) based on my contacts in the industry and related organizations. Some, but not all, participants were known to have worked on pregnancy-related issues in industry. This improved their ability to discuss the issue in depth. However, this may have introduced bias as they may have been more sensitive to issues about the inclusion of pregnant women than interviewees who have not worked on pregnancy-related issues. This may decrease the transferability of the findings. Care was taken to include informants who have worked on pregnancy-related issues and those who have not. I will consult with others in the field, including those on my dissertation committee, to identify potential qualified candidates. On the other hand, knowing me and my work in the industry may have caused participants to view me as an 'insider' and improved their comfort in speaking to me about this issue.

In the interview data analysis, the qualitative findings could be subject to other interpretations that may differ from my interpretation. In choosing participants from within and outside of industry, I hoped to add to the validity of the findings by using triangulation – examining evidence from different sources to see if similar themes are identified.<sup>229</sup> If so, it is

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<sup>229</sup>Creswell, J.W. (2003). Research Design: Qualitative, Quantitative, and Mixed Methods Approaches, (2<sup>nd</sup> ed). Thousand Oaks, CA: Sage Publications, p. 196.

likely I have identified valid themes. If not, participant's views may vary widely among my group of subjects or in this field of research.

c. Bias – As qualitative research is "fundamentally interpretive," personal reflection and the identification of the researcher's "biases, values, and interests," at the outset of the study is important.<sup>230</sup> As someone who has worked as a women's health care provider in practice, and as a researcher on pregnancy issues in industry, I bring background knowledge but also certain biases to this study. I acknowledge that I agree with proponents who seek a more rational and inclusive policy toward pregnant women in research studies. And I acknowledge that, while I will strive to maintain objectivity in the data collection and analysis, my biases may influence my findings.

#### **D. Plan for use of the combined study results**

##### **1. Improve knowledge:**

As I have been unable to find a source in the literature that quantifies the degree to which pregnant women are excluded from studies that might rationally include them, this study sought to reveal the extent to which this occurs. By rationally, I mean that the disease state being studied occurs in pregnant women and should be treated, and the drugs being evaluated are FDA pregnancy risk category A, B, or C. Is it standard practice to exclude pregnant women or are they sometimes included and how frequently does that occur? Are pregnant women systematically excluded from trials that study medical conditions that might occur during a woman's pregnancy and for which treatment should be administered? How

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<sup>230</sup>Creswell, J.W. (2003). Research Design: Qualitative, Quantitative, and Mixed Methods Approaches, (2<sup>nd</sup> ed). Thousand Oaks, CA: Sage Publications, p. 182.

many studies do not mention pregnancy in their exclusion criteria – and does that mean they are included or is it simply assumed that they would be excluded?

The quantitative review of the inclusion and exclusion criteria in clinical protocols provided this data. This information will raise awareness and add to our knowledge base in the field of obstetrical practice and clinical research. It will provide important information about the baseline of exclusionary or inclusionary current practices and make these practices explicit. This information will add weight to the dialogue about whether or not pregnant women are, in fact, excluded from participation in clinical research – and whether this should change.

The qualitative analysis will improve our knowledge of the current pharmaceutical industry perspective. What are the attitudes, beliefs, and practices of the industry and how do each influence company policy? What do representatives from organizations related to the pharmaceutical companies think about the issue? Do their opinions concur with or diverge from industry representatives? Are there opportunities for change? What are the barriers to change?

## **2. Improve policy and practice:**

FDA is currently conducting a final review of a draft guidance document that will make recommendations to industry about when and how to include pregnant women in clinical trials.<sup>231</sup> The industry will have the opportunity to provide feedback to the agency's plan within a constrained time period. Therefore, discussing the issues and potential solutions

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<sup>231</sup>FDA's Guidance Document To-Do List. (January 3, 2011). "*The Pink Sheet*".

ahead of the document's release for public comment will promote the potential for a reasoned and coordinated response.

As interested parties outside of the pharmaceutical industry deliberate on the risks and merits of including pregnant women in medical research, those within the industry may be unaware of the debate. Clearly industry needs to be part of this discussion.

To improve the health of pregnant women and their offspring by providing health care providers and pregnant women with accurate information about the risks and benefits of medical treatment during pregnancy is a rational goal. In order to do this, some stakeholders believe that more and better information is needed about the actual outcomes of pregnancies that utilized medications to treat conditions during gestation. In order to obtain this information we need to systematically collect the data from exposed pregnancies – in clinical trials, in post-marketing studies, or utilizing other methodologies. This study provides the perspective of experts working in and with industry about the barriers and facilitators to the collection of such data. In doing so, recommendations to company and regulatory policy are formulated that may serve to improve pregnancy outcomes.

## **Chapter 5**

### **Quantitative Results**

#### **Quantitative Study question**

What proportion of open U.S. pharmaceutical industry-sponsored Phase IV clinical trials currently enrolling women include pregnancy in their exclusion criteria?

#### **A. Background**

In order to protect the fetus from the potential adverse effects of experimental medical interventions and drugs in development, it has been general practice to exclude pregnant women from participating in clinical trials. An unintended result of their exclusion is that women with medically compromised pregnancies and their health care providers are often frustrated by the lack of clinical data available to inform treatment decisions regarding obstetric or non-obstetric complications.



It has been suggested that including pregnant women in clinical trials would result in better information about the safety and efficacy of treatment options during pregnancy by experts who are recommending their inclusion.<sup>232,233,234,235</sup> How extensive is the practice of excluding pregnant women? I was unable to find any documentation in the clinical literature of the current proportion of clinical trials that include or exclude pregnant women.

This study was designed to ascertain the proportion of clinical trials that exclude pregnant women by reviewing the inclusion and exclusion criteria of all U.S.-based, industry-sponsored open Phase IV interventional studies enrolling women of childbearing potential posted on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) between October 1, 2011 and January 31, 2012.

Phase IV trials are conducted using drugs that have already received regulatory approval and are currently marketed in the U.S. They evaluate issues about safety, concomitant medication interactions, use in populations other than those for which the drug was initially approved, etc.<sup>236</sup> Because these drugs have been studied in clinical trials, approved by FDA, and are on the market, more safety and efficacy information is available and the benefit-risk relationship is better established. These studies are, therefore, some of

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<sup>232</sup>Feibus, K. & Goldkind, S.F. (May 17, 2011) Pregnant women and clinical trials: Scientific, regulatory, and ethical considerations. Oral presentation at the Pregnancy and Prescription Medication Use Symposium, Silver Springs, MD.

<sup>233</sup>Mastroianni, A.C., Faden, R., & Federman, D. (Eds). (1994). Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine. Washington, DC: National Academy Press.

<sup>234</sup>Council for International Organizations of Medical Sciences. (2002). International ethical guidelines for biomedical research involving human subjects. Retrieved April 17, 2011 from [www.cioms.ch](http://www.cioms.ch).

<sup>235</sup>American College of Obstetricians and Gynecologists' Committee on Ethics. (2007). ACOG committee opinion: Research involving women. *Obstetrics & Gynecology*, 110(3), 731-736, p. 732.

<sup>236</sup>Spilker, B. (1996). Guide to Clinical Trials. Philadelphia: Lippincott Raven, p. 44.

the most appropriate studies in which pregnant women could participate. The exclusion of pregnant women from these studies will serve as a proxy for the practice of exclusion of pregnant women from all phases of clinical trials.

This study quantified the frequency with which pregnant women were excluded from current Phase IV clinical trials. To be included, the study must have been evaluating the treatment of medical conditions that could be experienced by, but are not limited to, pregnant women and they must not have included a medication that was in the FDA pregnancy category D (positive evidence of human fetal risk but benefits of use may outweigh the risk) or category X (positive evidence of animal or human fetal risk and the risk of use clearly outweighs the potential benefit). If there was no mention of pregnancy in the inclusion or exclusion criteria of a study, a study coordinator was contacted to confirm that pregnant women could be enrolled.

## **B. Results**

Application of the search criteria above retrieved a total of 559 studies from the ClinicalTrials.gov website as of 31Jan2012.<sup>237</sup> Of these, 4 were found upon closer examination to not meet the criteria specified – one was a trial for hemophilia limited to males and three were trials that were not sponsored by industry. This resulted in a total of 555 clinical trials available for study.

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<sup>237</sup> ClinicalTrials.gov is an open website, with clinical trials being added or removed on a continuous basis as new trials are initiated and completed studies are removed. Therefore, the number of trials retrieved on any given day may vary.

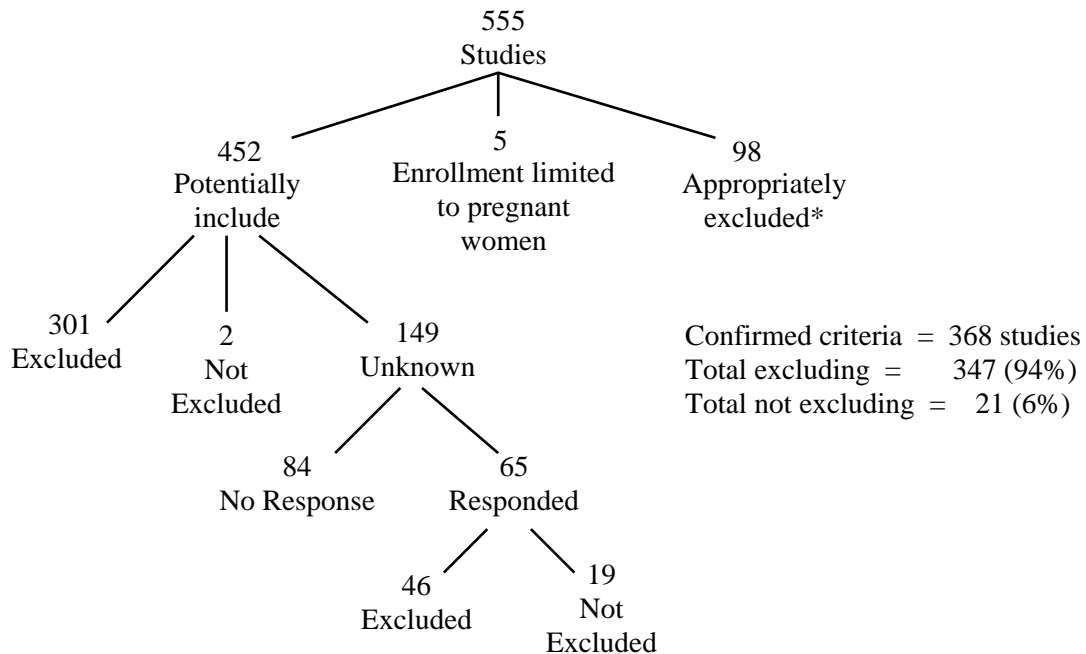
Of these 555, 103 were excluded from further analysis. Five (5) studies limited enrollment to pregnant women and 98 were found to appropriately exclude pregnant women based on the following justifications:

- N = 74 – At least one drug in study was in FDA Pregnancy Category D or X
- N = 17 – Age criteria excluded childbearing potential
  - 10 studies limited inclusion to men and women age  $\geq 60$
  - 6 studies limited inclusion to men and women age  $\geq 50$
  - 1 study limited inclusion to men and postmenopausal women age  $\geq 45$
- N = 4 – Study topic was menopause
- N = 2 – Study topic was contraception
- N = 1 – Study topic was lactation

Of the remaining 452 clinical trials that could potentially enroll women of childbearing potential, 301 specifically excluded pregnant women, 2 specifically did not exclude pregnant women, and 149 made no mention of pregnancy in the inclusion / exclusion criteria posted on ClinicalTrials.gov.

One might expect that, if pregnancy was not mentioned in the exclusion criteria, then pregnant women could be included. In order to test that assumption, all 149 of these studies' coordinators were contacted by phone, by email, or both. Eighty-four (84) did not respond to the request for information. Of the 65 studies for which we obtained clarification about whether or not pregnant women could be included, 46 (71%) actually excluded pregnant women and 19 (29%) did not exclude them from enrollment in the study.

**Figure 5.1. Number of studies available for review on ClinicalTrials.gov between 01Oct2011 and 31Jan2012 and their enrollment of pregnant women**



\* Pregnant women were excluded because the drug was in FDA Category D or X, or the age or topic (menopause, contraception, lactation) prohibited pregnancy.

Therefore, the overall results of the analysis were that, of the 368 clinical trials for which we had specific inclusion/exclusion criteria, 347 (94%) excluded pregnant women and 21 (6%) did not exclude pregnant women. Therefore, of the 368 Phase IV studies in which pregnant women could appropriately participate, we confirmed that 94% excluded and 6% did not exclude pregnant women from enrollment.

A range of medical conditions that could occur in pregnant women was included in the Phase IV studies evaluated. These included epilepsy, depression, fungal infection, arthritis, heart failure, peripheral artery disease, Von Willebrand disease, aneurysm, HIV, etc. None of the conditions were noted to never occur in pregnant women, though treatment of

some, like knee replacement, might be safely postponed until the completion of the pregnancy.

A comparison of the studies that were open to the enrollment of pregnant women to those that were not yielded little additional insight. In approximately 80% of the studies in both groups, the purpose of the trial was to evaluate treatment as opposed to prevention, diagnostic, or supportive care. Masking (or blinding) was also similar. The proportion of studies that were blinded (subjects and/or researchers do not know what treatment the subject is receiving) as compared to those that were 'open-label' (subjects and researchers know what treatment the subject is receiving) was also similar – 42% of studies were blinded in the trials that excluded pregnant women and 38% were blinded in those that did not.

The only variable noted to differ between the two groups was allocation – that is, whether the studies were randomized trials (in which subjects are randomly assigned to different treatment groups) or non-randomized trials (subjects may choose, or are in previously chosen treatment groups). In the 297 studies that excluded pregnant women and reported allocation on ClinicalTrials.gov, 75% were randomized and 25% were not. In the small number of studies (n=19) that reported allocation and did not exclude pregnant women, 58% of the trials randomized subjects into different treatment categories and 42% were non-randomized.

A comparison of the category of treatment being studied can also be made. There were six major categories: Drugs (n=245), Devices (n=77), Procedures (n=21), Biological Products (n=14), Diet (n=5), and Other (n=6). Excluding the last two categories whose numbers are too small to draw conclusions, the percentage of studies in each category that

excluded pregnant women was 98% of drug studies, 95% of studies on procedures, 87% of device trials, and 79% of biological product studies.

### **C. Discussion**

The answer to the question, "What proportion of open U.S. pharmaceutical industry-sponsored Phase IV clinical trials currently enrolling women include pregnancy in their exclusion criteria?" was, at first cut of the data, 67%. However, this number did not reflect the actual proportion of studies that excluded them. By contacting the study coordinators to confirm inclusion or exclusion, it was determined that the inclusion/exclusion criteria posted on ClinicalTrials.gov was inaccurate in regards to pregnant women – a key finding of this study. Only 2 studies specifically stated in their inclusion criteria that they included pregnant women.

Seventy-one percent (71%) of studies that did not list pregnant women in their exclusion criteria posted on ClinicalTrials.gov did, in fact, exclude them. This might infer that the practice of excluding pregnant women is so commonplace that it is simply assumed to be true and, therefore, did not need to be explicitly stated.

We contacted study coordinators for the studies that did not address pregnancy in the inclusion/exclusion criteria and asked them to clarify the protocol. Could pregnant women be included? Comments such as this one supported the assumption of exclusion:

*"We don't have to list every exclusion on ClinicalTrials.gov. No glaucoma treatments have been approved for use in pregnant women. So this [not to include pregnant women in the exclusion criteria] was a no-brainer."*

Other studies may not have specified pregnancy in the criteria because the condition was assumed to have a low prevalence in the treatment group, for example, certain age groups (adolescents, women over 40) or medical conditions (cardiomyopathy, dialysis). For example, one email response stated,

*"There is no specific pregnancy criteria in this study. The drug is mostly used in dialysis pts, who are generally unable (with rare exception) to become pregnant anyway. NOTE: Just because not excluded doesn't mean they will be included."*

This quote addresses the issue of de facto exclusion: pregnancy may not be an exclusion criterion, but that doesn't mean pregnant women will be enrolled. Pregnant women may not be recruited or accepted for enrollment in the study at the discretion of the Principal Investigator (PI).

But pregnancies do occur in many age groups and conditions so the protocols should be more explicit. Two studies addressed the need and the appropriateness of including pregnant women. One recognized that pregnancy would rarely occur in women with heart failure but had other studies to address that issue:

*"There is not a specific exclusion for pregnant women in [this] trial. However, this would be an extremely rare occurrence. ... We have other trials for pregnant women with cardiomyopathy."*

And the other was one of the two studies that explicitly included pregnant women in the inclusion criteria:

*"[Drug] carries a Category B pregnancy risk factor. Since this is a minimal pregnancy risk category, no special precautions will be taken to determine that the patient is not pregnant."*

This study found a higher proportion (75%) of the studies that excluded pregnant women were randomized trials compared to 58% of the studies that did not exclude pregnant women. Because the number of trials that did not exclude pregnant women is small (n=19), the strength of this finding is not robust and may be based on chance. But it would make sense that, if one were to enroll a pregnant woman in a study, it would have to be one in which she would expect to receive therapeutic benefit. In order for it to be ethically acceptable for her to enroll, the benefit would need to outweigh the risk to her, her pregnancy and her fetus, a somewhat higher hurdle than for non-pregnant subjects. Therefore, a non-randomized trial, where the subject was in a therapeutic group prior to the study or could choose what treatment group to join, would be preferable. This finding suggests that researchers who are conducting non-randomized clinical trials may be more open to the inclusion of pregnant women as study subjects.

It was not surprising to find that drug trials excluded pregnant women at a rate that is higher than that for other studies including those that assess procedures, devices, and biologics. The precaution against the testing of drugs on pregnant women is very well-entrenched (see Chapter 6. Qualitative Results for further discussion). However, the magnitude of the exclusion (98%) in these Phase IV trials, where pregnancy risk categories are defined, is higher than was anticipated by this author. Also of interest was the finding that 21% of the studies on biological agents did not exclude them. This may reflect our limited but disquieting recent experience with bioterrorism which has heightened society's concern for the protection and treatment of pregnant women in such dreadful scenarios. Whether it may also reflect an increased acceptance of the use of vaccines during pregnancy may be worth exploring. Two vaccines are currently recommended for administration during



pregnancy: H1N1 influenza vaccine and Tdap for tetanus, diphtheria, and pertussis (after 20 weeks gestation).<sup>238</sup>

#### **D. Limitations:**

It would be difficult to include an exhaustive list of conditions that would preclude a subject from being eligible for enrollment on the ClinicalTrials.gov website. Some study protocols addressed this issue by including statements such as "Additional inclusion (exclusion) criteria may apply", "Any subject who at the discretion of the Investigator is not suitable for inclusion in the study," or "Has any other clinically important abnormalities such that risk to patient of participation outweighs the potential benefit of therapy as determined by the investigator." Such statements leave the enrollment decision up to the individual PI. Contacting the study coordinators or Sponsors to confirm the number of studies that actually excluded pregnant women resulted in a more accurate assessment. A 94% exclusion rate confirms a very common practice.

Of course, all clinical studies should not include pregnant women. For example, studies for conditions for which treatment could be postponed might recommend deferral of enrollment until the conclusion of the pregnancy. This review did not attempt to exclude studies for conditions in which treatment can be deferred because, in many instances, that conclusion could be determined only by the patient and her health care provider. Severity of

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<sup>238</sup>March of Dimes. (2011). Vaccinations during pregnancy. Retrieved on March 15, 2012 from [http://www.marchofdimes.com/pregnancy/prenatalcare\\_vaccinations.html](http://www.marchofdimes.com/pregnancy/prenatalcare_vaccinations.html)

the condition, its effect on the patient's quality of life, and alternative palliative treatment options are factors that may need to be considered in that determination.

A potential limitation of the study is the omission of 84 studies that did not list pregnancy in the exclusion criteria and which therefore may have included them. We could apply the same ratio of exclusion to inclusion that we found for the 65 with confirmed criteria (71% vs 29%) to these 84 studies for which we were unable to obtain confirmation. That calculation would have added an additional 60 studies to the number that excluded women and 25 to the number that did not. This would result in an estimated total of 407 studies that excluded pregnant women and 45 that did not. Therefore, of the 452 Phase IV studies in which pregnant women could participate, we could *estimate* that 90% (95% CI = 82, 99) excluded and 10% (95% CI = 9, 11) did not exclude pregnant women from enrollment. Whether the actual proportion is the 90% we would estimate from this calculation or the 94% we confirmed - or somewhere in between - does not impact the results of the study: the exclusion of pregnant women from clinical research is clearly the norm.

The study was limited to Phase IV trials. Phase I trials were excluded because they only enroll healthy volunteers and would not be appropriate for pregnant women whose participation in research should be limited to those studies that potentially provide therapeutic benefit. Phase II and III studies were excluded mainly because information on the developmental drug's safety during pregnancy was not available in the public domain (toxicity study results are proprietary during development) or on the ClinicalTrials.gov database (the data source for this question). Therefore, I was unable to evaluate if pregnant women could have been appropriately included in such studies.

It is the position of this study that the exclusion of pregnant women from Phase IV studies of drugs and devices that are not contraindicated during pregnancy could serve as a proxy for the practice of the exclusion of pregnant women from all phases of clinical trials. This assumption could be challenged. One could ask, "Why would a pregnant woman participate in a clinical trial when she could get the drug on the market? Don't people participate in clinical trials so that they can access a drug that is not otherwise available?" Research has shown that people participate in clinical research studies for many reasons including access to otherwise unavailable treatments. Other motivations include: "closer monitoring than in routine practice, getting attention for other ailments, better physical and laboratory health checks, superior physicians, labs, and testing, more contact with the providers,....remuneration, and contributions to society."<sup>239</sup>

Of course, since pregnant women have not been included in clinical studies, we don't know to what extent they would volunteer to participate. It needs to be re-emphasized that pregnant women should only be asked to participate if they are in need of treatment and the study would potentially provide therapeutic benefit and if the potential benefits of the study exceeded the potential risks. Under those circumstances, participation would be very much like treatment in clinical practice with the added benefit of improved informed consent, enhanced pregnancy monitoring, and the patient's knowledge that she has contributed her experience to the accumulated medical knowledge base to assist other pregnant women.

However, a limitation of this study is that the exclusion of pregnant women from participation in Phase I, II, and III studies was not measured and that their exclusion from

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<sup>239</sup>Iber, F.L., Riley, W.A., & Murray, P.J. (1987). *Conducting Clinical Trials*, New York: Plenum Press. In Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 378.

Phase IV studies may not reflect their exclusion from earlier phases of clinical research. In addition, the study evaluated studies posted on ClinicalTrials.gov at a specific point in time. This time period may not reflect the same prevalence of inclusion/exclusion at other points in time.

This study does not address whether pregnant women would be willing to enroll in clinical studies, nor if they would be more or less likely to enroll in Phase IV studies than in Phase I, II, or III studies. More research should be done on this topic. Studies have shown that pregnant women tend to overestimate the risk of environmental exposures (including drug exposures), which suggests they would be less inclined to participate in clinical research. However, some pregnant women would likely participate in Phase IV studies for the same reasons that some non-pregnant people would: to help others by advancing scientific knowledge, to improve their own health care treatment and monitoring, to gain access to affordable treatment, etc. One small study found that 95% of pregnant women interviewed said that they would participate "if there is a chance that participation in a clinical trial would help their pregnancy and improve their baby's health."<sup>240</sup> Further research is needed to confirm or refute this finding.

## **E. Conclusion:**

Phase IV trials are conducted using drugs, devices, and other treatments that have received regulatory approval and are currently marketed in the U.S. Phase IV studies are

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<sup>240</sup>Rodger MA, Makropoulos D, Walker M, Keely E, Karovitch A, and Wells, PS. Participation of pregnant women in clinical trials: Will they participate and why? *American Journal of Perinatology* 2003; 20(2):69-76.

conducted for various purposes including, but not limited to, evaluating safety issues, long-term effects, cost-effectiveness, and use in populations or for conditions other than those for which the drug was initially approved. Because these drugs and devices have been studied in clinical trials, were approved by FDA, and are on the market, safety, efficacy, and the benefit-risk relationship are better established. These studies, therefore, are some of the most appropriate studies in which pregnant women could participate.

Women with medically compromised pregnancies and their health care providers can be frustrated by a lack of clinical data available to inform treatment decisions. Subject matter experts state that including pregnant women in clinical trials would result in better information about treatment options during pregnancy. The clinical literature did not provide any documentation or estimate of the current proportion of clinical trials that exclude pregnant women.

Obtaining a measure of the extent of their exclusion is complicated by the fact that it would be inappropriate to include pregnant women in some trials because the drug being tested may be harmful to the woman, her pregnancy, or her fetus. During drug development, the toxicology data on safety of use during pregnancy is proprietary and is known only to the drug developer. So the number of Phase I, II, and III trials that exclude pregnant women on ClinicalTrials.gov would not take into account whether it was appropriate to do so. In order to estimate the proportion of clinical trials that exclude pregnant women but could include them, this analysis was limited to Phase IV studies, where the impact of the intervention on pregnancy has been evaluated during the FDA approval process. Studies of drugs, devices, and procedures that are not contraindicated during pregnancy would be those most appropriate to include pregnant women.

It is the position of this study that the exclusion of pregnant women from Phase IV studies of drugs and devices that are not contraindicated during pregnancy can serve as a proxy for the practice of the exclusion of pregnant women from all phases of clinical trials. This study establishes that approximately 6% of current industry-sponsored trials include pregnant women among the populations eligible for enrollment. However, the overwhelming proportion (94%) of studies that exclude pregnant women suggests that, even when it may be appropriate to include them, the practice of excluding them is very well-established.

## **Chapter 6**

# **Qualitative Results and Discussion**

### **QUALITATIVE RESULTS**

This study sought to isolate the perspectives of key informants within the pharmaceutical industry and related organizations, using qualitative key informant interviews to identify rationales for the exclusion of pregnant women from clinical research and to discover opportunities for their inclusion.

#### **Qualitative Study Question**

What are the current perspectives of U.S. pharmaceutical industry representatives and those of related organizations about the inclusion of pregnant women in clinical research studies?

#### **A. BACKGROUND**

To obtain Key Informant information, 16 semi-structured interviews were conducted with subject matter experts in the U.S. pharmaceutical industry, and related organizations:

1. Staff from clinical development, safety, regulatory, and epidemiology departments in U.S. pharmaceutical companies (n=5) and biotech firms (n=3)
2. Legal counsel from pharmaceutical companies (n=2) and PhRMA (n=1)

3. Pharmaceutical Research and Manufacturers of America [PhRMA] (industry professional association) representative (n=1)
4. Independent Institutional Review Board members who are contracted by industry to review clinical research protocols (n=3)
5. Food and Drug Administration representative (n=1)

Note: BIO, the biotechnology industry association, was invited but declined to participate in the interviews.

Interviews were conducted by telephone. Study questions were provided prior to the interviews which were scheduled at the participant's convenience. It is important to note that study participants were speaking on behalf of themselves and were not representing the position of their companies or organizations. I provided assurance that their names would be kept confidential. With their permission, 14 of the 16 interviews were recorded (2 lawyers declined). The recordings were then transcribed using Dragon Naturally Speaking® voice recognition software. Transcripts of the interviews were copied into the Centers for Disease Control and Prevention (CDC) EZ-Text® software which is utilized for the management and analysis of semi-structured qualitative data sets. Coding was applied to the interview data to facilitate recognition and retrieval of common themes.

The most pertinent findings from the interviews are presented below. For more information on these findings see Appendix IV. Qualitative Study Results: Key Findings from Key Informant Interviews.



## **B. STUDY RESULTS AND DISCUSSION**

The primary purpose of this study was to identify from key informants in the pharmaceutical industry and related organizations their perceived rationales for the exclusion of pregnant women from clinical research and to discover opportunities for their broader inclusion. In addition, the 2009 Second Wave Consortium workshop had identified two key missing pieces of information for which this study sought clarification: "What is the strength of industry's role in affecting the outcome of the debate on the inclusion of pregnant women in clinical trials?" and "How influential is the industry's perceived risk of litigation – and is it a real risk?" The key informants provided insights on each issue as discussed below.

The results of the quantitative study (see Chapter 5) revealed, as was expected, that most clinical research in the U.S. today excludes pregnant women from participation. Participants in the qualitative study agreed that excluding pregnant women from clinical studies was the well-established norm.

The key informants perceived that, of the three primary stakeholders - the pharmaceutical industry, IRBs, and FDA - the pharmaceutical industry has the most control over whether or not pregnant women are included as study subjects because they:

- decide if they want to sponsor the trial or not
- are the owner of the protocol and makes the initial eligibility criteria decisions
- are the driver of what is to be accomplished by the study
- know the science behind the drug in development
- are the responsible party and bear the burden for any "drug exposure-perceived injury"

Four stakeholders were identified by key informants as having the power to veto a clinical trial: the trial's sponsor, the FDA, the IRB, and the institution at which the trial is to take place. All of these stakeholders were perceived to be resistant to the idea of including pregnant women in clinical trials. FDA was found to have the least influence as there is no regulatory statute that requires the exclusion of all pregnant women from all clinical trials (they may be included under certain circumstances). IRBs were felt to be a potential barrier to inclusion based on their cautious nature, their patient-centric focus, and the variability of decisions from one IRB to the next.

Having established that the pharmaceutical industry is one of the most important stakeholders in the effort to increase the participation of pregnant women in clinical research, the participants were asked to discuss the reasons why the industry may and may not want to include them.

### **1. Reasons for Exclusion / Barriers to Inclusion**

Rationales against the inclusion of pregnant women in clinical trials identified in the Literature (see Chapter 2: Literature Review) overlapped with the concerns raised by the industry stakeholders: non-maleficence and litigation, enrollment issues, business concerns, and the lack of a regulatory mandate for their inclusion were all cited as rationales for exclusion in both the literature and in this study. Non-maleficence and litigation were the most-cited rationales from both sources.

**Can you give me 3 or 4 reasons why a Company or organization would not want to include pregnant women in clinical trials?**

*"I can't think of 3 or 4 reasons why you'd want to include pregnant women."*  
 -- pharma company lawyer

By far, the two predominant answers to this question were the desire to do no harm and the risk of litigation. Most participants mentioned one or both. Other commonly cited reasons to avoid including pregnant women were scientific validity issues, risks to drug approval and to company reputation, and the increased complexity of conducting such trials. Other reasons mentioned by one or two participants were the lack of advocacy for – or even awareness of – the need for their inclusion, the lack of a regulatory requirement or recommendation, and that it is the historically acceptable way to conduct research.

**Table 6.1 Participants' reasons why pregnant women are not included in clinical trials**

<b>Most Cited</b>	
Do No Harm	
Litigation Risk*	
<b>Commonly Cited</b>	<b>Occasionally Cited</b>
Scientific validity issues	Lack of advocacy for/awareness of issue
Risk to drug approval	Risk to drug market
Risk to company reputation/negative publicity	Lack of regulatory requirement or recommendation
Increased complexity of the study	Not the norm/never been done
Business concerns	Lack of fetal consent
<b>Areas of confusion</b>	
Are there regulations against inclusion?	
What is the extent of, and what are reasons for, medication use by pregnant women?	
What are the risks of research, in general, and are pregnant women more vulnerable?	

\*Litigation concern is addressed in the Section 3.

a. Do no harm: beneficence and non-maleficence

*"the risk to the fetus... is a historically insurmountable hurdle."*  
-- pharma company lawyer

The interviewees agreed that the most important deterrent to the inclusion of pregnant women in clinical trials is the fear of doing harm to a developing fetus. Most other considerations stemmed from that fear. Being overly cautious was a position that the industry has been comfortable with.

From a company lawyer –

*"I think it's first and foremost the ethical considerations of enrolling a woman when you presumptively don't have a clear sense of the potential teratogenic effect of product. So, historically, there's been a very strong reluctance to enroll pregnant women for fear of causing harm to the unborn fetus. That's the primary [reason]. I think that would be far and away the most important."*

Another company lawyer agreed,

*"the risk to the fetus... is a historically insurmountable hurdle."*

Three pre-requisites to drug testing in pregnant women were identified by the participants:

- Prior knowledge of the drug's safety for use during pregnancy
- Prior knowledge of its efficacy against the medical condition in question
- Prior knowledge of the proper dosing to achieve therapeutic benefit

*"The problem lies in the fact that during a clinical trial, we don't know the safety of the drug, that's why we're doing the clinical trial. That's why we're doing the trial. So, under this kind of legal susceptibility, this volatile field, in the context of not knowing the benefit of the drug yet and not knowing the safety of the drug yet,*

*then it makes sense that we would exclude this very susceptible population until at least the benefits are known. And we will not know the benefits of the drugs until the end of the phase 3 trials. We may think we know them but until we do the big clinical studies we don't really know the benefits of the drug, the true efficacy and benefits."*

-- pharma physician

*"It's not just congenital anomalies or the effect on the pregnancy, the question is, what's the proper dose? Pregnant women get increased blood flow and hemodynamic changes that take place in pregnancy. I think we need to do some pharmacokinetic studies to make sure that the dose is the correct dose for pregnant women. If I expect efficacy, I want to make sure I have the correct blood levels to get that efficacy."*

-- pharma physician

b. Scientific validity: Data interpretation

*"Pregnancy is just an outlier."*

-- biotech physician

Drugs are tested in clinical trials to gain data from experience in enough people to result in statistically significant information to draw conclusions about the drug's efficacy, safety, and dosage for use in a general population. The people who are eligible to be included in the studies are fairly closely proscribed to exclude people who may make analyzing the data more difficult – people who have other medical conditions than the illness the drug is intended to treat, people who are taking other medications that may interact or interfere with the study drug, etc. A rationale for the exclusion of pregnant women articulated by the participants in this study was that pregnant women may complicate the interpretation of data if they were included in studies of drugs for the general population.

*"...they are so much of an outlier in terms of the normal physiology so they just exclude them. They exclude patients who have got too complicated a medical history, or who are taking too many concomitant meds. That's really basic." Another participant said, "It's the same thing that honestly drives really narrow patient*

*populations in the studies they do anyway... pregnancy is just an outlier on that spectrum."* -- biotech physician

Pregnant women were cited as having a unique physiology that could impact drug studies in two ways:

- Drugs may affect pregnant women differently than non-pregnant women.  
(pharmacodynamics)
- Pregnant women may affect drugs differently than non-pregnant women.  
(pharmacokinetics)

It was felt that these factors need to be considered and that they should be evaluated in the context of a study designed for pregnant women rather than including pregnant women in a study designed for the general population. Also, if pregnant women were included in general population studies, the numbers enrolled would likely be low and would probably result in a lack of interpretable data to make recommendations for use of the drug in pregnancy.

*"We want to make sure that research is always scientifically valid. If not, then you're putting people into research that does not have a possibility of having some benefit in the future, so then it's not ethical to include people in such a trial."* -- IRB representative

Therefore, one of the key findings of this study is that industry perceives it to be preferable to design studies that specifically target pregnant women rather than include pregnant women in clinical studies designed for the general population. These studies would best be conducted after initial testing has established low risk of toxicity and teratogenicity in

animal tests, efficacy in the general population, and proper dosing in each trimester of pregnancy.

c. Evaluating teratogenicity:

*"Thalidomide has really scared a lot of companies"*  
-- pharma physician

Enrolling pregnant women in research studies was seen by the participants as a complex and ill-defined process complicated by the fact that between 2% to 4% of pregnancies in the background population result in an infant with a major congenital anomaly. That percentage rises to about 15% when you include minor anomalies – those with no medical or only minor cosmetic significance. The causes of these anomalies are, in the great majority of cases, unknown. Those attributed to chemical exposures, including but not limited to drug exposures, are very low (about 1%).<sup>241,242</sup>

Therefore, if you include pregnant women in studies, a certain number of infants will be born with birth defects just by chance or background occurrence. The risk cited by the study participants is that a spontaneous birth defect could be erroneously attributed to the drug exposure. The evaluation of the potential teratogenic effect of a drug on a fetus follows a well-defined scientific analysis that includes factors such as the gestational timing of the exposure in relation to the fetal development of the organ system affected, the effect in

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<sup>241</sup>U.S. Department of Health and Human Services, Food and Drug Administration. (2005). Reviewer guidance: Evaluating the risks of drug exposure in human pregnancies. Retrieved from <http://www.fda.gov/cder/guidance/index.htm>; citing Koren G, Pastuszak A, and Ito S. (1998). Drugs in pregnancy. *New England Journal of Medicine*, 338(16), 1128-1137.

<sup>242</sup>Brent, R.L. (2007). How does a physician avoid prescribing drugs and medical procedures that have reproductive and developmental risks? *Clinics in Perinatology* 2007; 34:233-232, p. 234.

relation to the dosage, the consistency of the effect, etc. A teratologist will be able to provide a detailed analysis of the strength of the association between the drug exposure and the birth defect, but, especially when there are only a few cases, it is difficult to have certainty of causation. In fact, certainty of causation is easier to assure than certainty of non-causation. And despite the scientific evidence, causation could be attributed to the drug in the mind of the public, sometimes assisted by the legal community. This is what happened with the drug Bendectin (discussed in Chapter 1), an effective and non-teratogenic drug that was removed from the American market because of litigation costs. The participants in this study disclosed that pharmaceutical companies are cautious about testing a new drug in pregnant women and risking its reputation in the marketplace if there is no mandate to do so.

*"Because, as you well know, bad things happen sometimes in pregnancies even when no drugs have been taken. So having one of those rare, but not clearly drug-related events happening could cast a negative shadow on a drug forever and even prevent approval. So having one or two birth defects occur, even if they were background, you wouldn't have enough data to clearly say it was background, and it could really kill the drug."*

-- pharma physician

*"I would not want the drug I was trying to develop to be tagged as being harmful to women who might become pregnant, [or] being blamed for spontaneous abortions or congenital anomalies. Part of the problem with enrolling just a couple hundred people is that you don't know how to interpret the data. You don't know if there's an association or not. The drug could be blamed for it one way or the other and I think that's unfortunate."*

-- pharma physician

d. Regulatory rationales:

*"It's just like a black hole."*

-- biotech physician



There appeared to be some confusion about what local and international regulations allow and don't allow. Some respondents thought that FDA regulations barred the inclusion of pregnant women in clinical trials, others thought that European regulations did so. Some thought the human rights documents like the Belmont Report or the Declaration of Helsinki prohibited their inclusion. A biotech physician cited *"different regulations from the time of the Helsinki Declaration until now not allowing...the participation of pregnant women in clinical studies"* as the reason for their being excluded.

Some participants stated that pregnant women were not included because FDA, or other regulatory bodies, do not require – or even recommend – that developmental drugs be tested for use in pregnancy. Few participants even knew that there was a draft FDA guidance being developed on this subject.

An FDA employee predicted that the companies are

*"not going to go there, quite frankly, because they're not regulated to go there and there are other special populations, like kids, that they're going to have to go to first."*

One physician, who has worked at two 'Big Pharma' companies and a biotech firm stated,

*"Nobody even talks about it in your planning a study. It's just like a black hole. These days when you go [to FDA] for scientific advice when you're doing a program, you're looking at pediatric patients, they're pushing a lot for elderly patients, and it's not even on the radar screen about pregnant women."*

Another regulatory issue raised was product labeling. Currently, because most drugs on the U.S. market are not tested on pregnant women and animal study results may be

ambiguous, they are labeled FDA Pregnancy Category C, which states that, 'human studies are lacking, animal studies have shown a risk or are lacking as well, but the potential benefit may outweigh the potential risk.' Because pregnancy data are not collected for the purpose of adding information to the label, even when products have been on the market for years, most remain a Category C for the lifetime of the product. One respondent questioned the quality and usefulness of the data in the current labels and inferred that data collected from actually studying pregnant women would improve the information in the label and the ability to treat medically compromised pregnancies more efficaciously.

e. Business concerns:

*"I'm glad this is anonymous."*  
-- pharma physician

Pharmaceutical companies are for-profit entities whose mission is to create and market drugs, biologics, and medical devices that prevent, treat, or suppress the adverse medical conditions that plague humanity. That mission includes making a profit in order to compensate the people who work to achieve the mission and to spur the continued research required to sustain innovation and grow profitability.

For the pharmaceutical company, the ultimate purpose of the clinical trial is to confirm the efficacy and the safety of the new compound in order to get their product approved as quickly as possible. Years of research and millions of dollars have already been spent in shepherding the potential product to the clinical trial stage.

*"Companies want to get their studies approved as fast as possible, they don't want any extraneous issues that could go wrong."*  
-- biotech physician

*"Industry constantly thinks about the risk to the drug."*  
-- pharma physician

Populations that are peripheral to the primary target population are a secondary concern. On this topic, key informants stated that,

*"They're not going to go there until they know this drug is going to make money for them,"*  
-- FDA representative

*"[T]hey don't want to put their drug in a position where the drug may receive an unfavorable review from the FDA or any regulatory party."*  
-- pharma physician

New drug approvals are based upon the results of Phase I through Phase III trials in the general population. Delaying testing in pregnant women until the conclusion of the Phase III trials was perceived to be a potential solution to the risk of having a chance finding or a false association with a birth defect interfere with an effective product's initial approval.

In the context of business, several participants named adverse notoriety for the company as a reason to avoid testing the drug in pregnant women. An IRB representative said, *"[I]f something were to go wrong and people found out, 'wow, you were testing this drug on pregnant women...'"* the impact to the company's reputation could be significant and difficult from which to recover.

*"It's not just the fear that something can go wrong – I'm glad this is anonymous – [but] when you consider that things can go wrong in a clinical trial and the most published news about clinical trials is the negative information... You conducted a clinical trial and something goes horribly wrong, the name of the facility is put out*

*there, the name of the physician that conducted it is put out there, the IRB that reviewed and approved it is put out there...even as careful as you can be.."* -- pharma physician

f. The risks of research and pregnancy

*"It's risky research."*

-- IRB representative

Some interviewees gave me the impression that they perceived the risk to the pregnant woman and the fetus from participation in *any* clinical trial to be extremely high. They did not consider it on a case-by-case or a trial-by-trial basis, but thought the risk to be very high across the board, e.g.,

*"Extreme safety risks – for the mother and the unborn child." "It's risky research. I consider it risky research."* -- PhRMA lawyer

And they suggested that pregnancy itself was a high risk condition,

*"Not only is the woman's body different, [but it is] potentially more vulnerable healthwise while pregnant..."* -- IRB representative

Research has shown that pregnant women and health care providers overestimate the teratogenic risk of drugs and environmental factors. Do we also overestimate the risk of participation in clinical trials by pregnant women? Also, are women less healthy and more vulnerable when pregnant? Is pregnancy a disease state or a healthy state? Are pregnant women, as the Common Rule suggests, a vulnerable population?

- g. The informed consent of the fetus

*"The child has no voice."*

-- IRB representative

A couple of the participants suggested that one of the reasons why pregnant women are not included in clinical trials is because it is impossible to consent the fetus. IRB informants stated:

*"There's not just one person, there's two people at risk. You have your second person at risk that has no voice whatsoever. You have the mother who can say, yeah, I think I want to do this, but when she says that, she's speaking for a child as well, and the child has no voice. I think that's the hardest part."* -- IRB representative

*"Whatever you think of the moral status of the unborn human life, medicine can treat the fetus...as a patient and the law tends to as well. So in practice there's a human being there, who in terms of human subjects protection is by definition vulnerable."* -- IRB representative

The status of the fetus as an entity whose needs, it was suggested, should be considered as independent from the pregnant woman was raised in the responses to this study and could be considered to be a barrier to the inclusion of pregnant women in clinical trials.

- h. Limit testing to drugs indicated for use by pregnant women

*"[T]here's actually a risk of non-treatment to the fetus as well."*

-- pharma company lawyer

*"I can't think of 3 or 4 reasons why you'd want to include pregnant women - unless it's a situation where you have a specific case where you need to study your intervention in the setting of pregnancy because pregnant women are going to get your drug in the (post-marketing environment)." -- pharma company lawyer*

This response suggests that pregnant women will only use a drug that is intended for use by pregnant women. We know that many exposures in pregnant women are unintended – the use of medication by women who do not yet know that they are pregnant. We also know that many medical conditions are not specific to pregnancy but may occur in pregnant women. Therefore, it is difficult to determine with any specificity, which drugs in development will or will not be used by pregnant women. The prudent assumption would be that most drugs, if they are effective, will be used by pregnant women.

Since it would be impossible to know what drugs may be used by pregnant women in the market place, are there others ways to target research for pregnant women?

*I doubt that there's going to be much interest in sponsoring clinical trials for the use of chronic meds for non-life-threatening conditions or where there is a reasonably well-established treatment paradigm. I mean, you have insulin for diabetes, you have 'suffer with your symptoms' for allergic rhinitis, etc. A lot of these, you can kind of manage through, but there's others that as a pregnant woman you can't always wait. And there's actually a risk of non-treatment to the fetus as well. Then I think you have a much more compelling ethical argument for experimentation.*

*-- pharma physician*

i. Lack of advocacy

*"[T]here's just been no interest in looking at this. There's not been anyone to advocate for it...It's not very high up in the consciousness of most people conducting clinical studies."*  
-- biotech physician

There has been no push for a change, no pressure on industry to do this. The lack of experience, the perceived hassle, the increased complexity of the study design, IRB resistance, legal considerations, all conspire to maintain the status quo. One participant summed it up in this way,

*"I think there's a long history of not doing it, so trying to get over the inertia of doing that is very difficult."* -- biotech physician

And yet, there are suggestions, like the draft FDA guidance and the Second Wave Consortium, that advocacy has begun. From the FDA representative –

*"they have to get over the sort of natural reaction of, 'oh, boy, we really can't do this' and then get down to the fact that, 'yes, we can do it, how are we going to do it?'"*

**Key Findings for Section B.1.: Reasons for Exclusion / Barriers to Inclusion**

One of the aims of this study was to isolate the **concerns** that are articulated by the pharmaceutical industry and their IRB and FDA colleagues regarding the inclusion of pregnant women in clinical trials. A better understanding of the potential barriers perceived by these powerful stakeholders can contribute to the formulation of a plan for change.

Key finding #1: The fear of causing harm to a fetus is the most important concern limiting the inclusion of pregnant women in clinical trials.

Key finding #2: The fear of litigation is one of the major concerns that is limiting the inclusion of pregnant women in clinical trials.

Key finding #3: The efficacy, safety, and proper dose of a medication must be known to some extent prior to testing the drug in pregnant women.

Key finding #4: Industry has little experience designing clinical trials that include pregnant women. More information is needed to assist with the design of such studies.

Key finding #5: National and international regulations regarding the inclusion of pregnant women in clinical studies are not well understood.

Key finding #6: Studying drugs in pregnant women would provide valuable information for the label, which would improve the treatment of pregnant women.

Key finding #7: Industry is reluctant to risk the approval of a drug for the non-pregnant population or the reputation of its company by testing drugs on pregnant women.

Key finding #8: A sufficient number of pregnant women must be included in a study of pregnant women to ensure that the data collected is interpretable.



Key finding #9: Industry perceives little motivation or advocacy for the study of its products in pregnant women.

## **2. Litigation**

### **2a. Litigation Risk**

**Do we know that allowing pregnant women in clinical trials would result in litigation or are we presuming it would?**

*"The elephant in the room is litigation."*

-- biotech physician

Most of the participants raised the issue of litigation during the course of the interview. Most of the respondents to this question stated that they presumed that liability would increase if we conducted clinical trials in pregnant women, but they were not sure that it would increase. Since we have little experience with trials in this population, we really do not know.

*"...when you talk to the OB people,... I hear that there are a lot of malpractice suits concerning congenital anomalies..."*

-- pharma physician

Of the two participants who said they know that litigation would increase, one biotech physician said he knew it because of reports in the media and the other, a pharma company epidemiologist knew it from personal experience at her company. The latter's experience was in regards to a product that was on the market for years and was subsequently found to raise the risk for certain birth defects.

The biotech company physician said, "*people are suing already when we are excluding them.*" When asked to explain, he said that his company has been involved in litigation concerning the exclusion of a woman from a trial during which she became pregnant and one concerning a pregnant woman who was excluded from enrolling in a clinical trial, because they are "*not providing them with the drug that they think is necessary.*"

A representative from PhRMA stated that, "*there are not a lot of lawsuits filed with respect to clinical trials*" in general. This is corroborated by the literature which indicates that, "the risk of incurring liability during the early stages of drug investigation is actually quite small whereas the potential for substantial liability is much greater once a fetotoxic drug enters widespread use."<sup>243</sup>

The issue of informed consent was raised by several participants such as this pharma company lawyer who said,

*"if they had informed consent, I can't really see a huge risk of litigation versus other studies that we do."*

An IRB lawyer responded that,

*"you're following the regulations, you obtained IRB approval so it's been considered from an ethics perspective, the person's been informed about it, the risks have been minimized as much as possible, and you're doing it to help pregnant women right there in the trial or in the future."* A potential increase in litigation, he said, "*should not be a reason to stop people from including pregnant women in clinical trials. I don't think there's going to be that much of a boom in litigation for the industry.*"

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<sup>243</sup>Clayton, E.W. Liability exposure when offspring are injured because of their parents' participation in clinical trials. (1994). In Mastroianni, A.C., Faden, R.R., & Federman, D.D., Women and Health Research: Workshop and Commissioned Papers (pp. 102-112). Washington, DC: National Academies Press. Retrieved March 11, 2012 from <http://www.nap.edu/openbook/0309050405/gifmid/103.gif>

Citing the anthrax study, an IRB lawyer stated that, "*pregnant women are being included in this trial for a very important reason just like people who are not pregnant are included in clinical trials.*" But not everyone agreed. A pharma company lawyer said that

*"the decision to sue is something that the Company can't control. I would make sure the informed consent is as strong as it can be and Investigator's Brochure contains disclosures of all data to date about risks. It would be a benefit/risk analysis. We can defend on causation," he continued, "bring in experts, particularly to discuss the science behind the defect. But when playing to a jury – I have [children] – any juror might see the case as a parent with a child [would]. So I think the litigation risks are higher."*

### **Key Findings for Section 2a. Litigation Risk**

Because birth defects occur at a rate of 3 to 4% in the general population, birth defects would therefore be likely to occur in 3 to 4% of the infants born to women who participated in clinical trials. The expectation among many participants was that litigation would follow these adverse events. But, upon further discussion, it was acknowledged that, since we have little experience with pregnant women in clinical trials, we really don't know.

Key Finding #1: There is a perception that the risk of lawsuits against a company would be higher if drugs were being tested on pregnant women. But, because we have little experience in this area, we don't know if the litigation risks would be higher in clinical trials of pregnant women than in clinical trials in general.

Key Finding #2: There is also a perception that excluding pregnant women from clinical research could result in litigation due to adverse pregnancy outcomes caused by denying

pregnant women access to a developmental drug they needed, or caused by a drug that was not fully evaluated before entering the market.

Key Finding #3: Thorough informed consent, complete disclosure in the Investigator's Brochure, FDA approval, IRB review, risk minimization activities, and the disclosure that the trial is intended to help pregnant women now and in the future, could help protect the company from lawsuits in clinical trials of pregnant women.

Key Finding #4: Our litigious society, the emotional component in jury trials, and increased litigation risk in the obstetrical community in general could increase the risk of litigation in clinical trials of pregnant women.

Key Finding #5: The risk of liability for injuries that occur during research in general is low. Some respondents, including company lawyers, believed that the increased risk would be minimal and should not be a deciding factor in whether or not to conduct trials in pregnant women.

## **2b. Litigation Environment**

**Do you think litigation is higher in the clinical trial environment or in the post-marketing environment?**

*"We're risk averse...to anything that has to do with a potential lawsuit."*  
-- biotech physician

The participants of this study expressed concerns about the potential for litigation against the pharmaceutical companies and how it could impact research and product

availability. Most respondents thought that the risk of litigation was lower in the clinical trial environment than in the post-marketing environment, followed closely by those who answered, "I don't know."

Only three participants thought that the risk of being sued was lower in the post-marketing environment. The concept of the 'learned intermediary' was mentioned by a pharma physician who said, *"in the post-marketing environment the prescribing physician has the decision-making responsibility,"* and a pharma lawyer who said that for marketed products, *"you're going to have a labeled statement about use in pregnancy...and the prescribing physician will have made the judgment about that in light of the known risks."*

The third respondent, a biotech physician, thought the risks were higher during clinical trials because you know less about the safety of the drug at that point in time. He felt that the drug being studied could be associated with spontaneous abortions or birth defects that occurred during the trial by chance. The pharma physician stated that, *"as soon as the Company is involved, automatically you assume that there is a greater risk,"* but, he acknowledged, *"It's a guess."*

**Table 6.2 Factors that increase the risk of litigation by environment**

<b>Factors that increase the risk in the post-marketing environment</b>	<b>Factors that increase the risk in clinical trials</b>
No informed consent	Little knowledge about the safety of the drug being studied
Lack of adequate testing / due diligence in clinical trials prior to marketing	No regulatory statement about safety (like the drug label)
Many more pregnant women will be taking the drug in an uncontrolled, uninformed manner. They may have concurrent medical conditions or be taking concomitant medications; have less instruction on the proper use of the product and less monitoring for safety and efficacy.	No learned intermediary prescribing the product
	Current standard of care is exclusion – why were they testing pregnant women?

**Table 6.3 Factors that decrease the risk of litigation by environment**

<b>Factors that decrease the risk in post-marketing environment</b>	<b>Factors that decrease the risk in clinical trials</b>
Learned intermediary (prescribing physician)	Informed consent
Drug label	Drug is known to be experimental
Drug was approved by FDA	Study conducted according to regulations
	IRB acknowledgement that risks were minimized and study design is ethical
	Study is conducted for the benefit of pregnant women
	Legal scrutiny of the protocol prior to implementation
	Select population in trials
	Historical precedent – it is harder to succeed with litigation in the clinical trial setting than in the post-marketing setting

Most of the interviewees thought that the risk of litigation was higher in the post-marketing environment for the reasons shown in Tables 6.2 and 6.3. They felt somewhat protected by the assumption that people participating in clinical trials were aware that the drug was experimental. When the drug is on the market, they felt that the public assumption is that the drug has been shown to be safe and effective and it is used by a larger and more diverse group of people. These factors could increase the risk for adverse pregnancy outcomes that could result in litigation.

*"I actually think the litigation risk would be higher in the post-marketing environment. The clinical trials are being conducted according to regulations, being reviewed by an IRB, people are going into the study being informed about potential risks, and people are in the trials being conducted for the benefit of the specific people or...pregnant women. It'll be much more difficult to make a case [for] the mother or the fetus who was harmed in the clinical trial setting. Now if you take that in the post-marketing setting, where you have this drug that's been approved by the FDA and now it has some deleterious effect on the pregnant woman or it's not effective, everyone's going to come down and say, "how, FDA, could you let this be approved?" and also, "how, Sponsor, can you allow this to go to the market? You didn't do your due*

*diligence, you didn't do your research to see if it would affect pregnant women, to see if it would be safe." I think now you have much more firepower to say you didn't do everything you should have, you didn't do due diligence, you breached your duty, therefore we can make a good case against you." -- IRB lawyer*

*"Litigation risk seems to be higher in the post-marketing stage, because of the fact that in clinical trials, you have a very select population. You have a smaller population... in order to get a drug approved. And [when] they're using the drug in post-marketing and it goes into widespread use there – many, many, many more patients – and patients who don't necessarily... fit the profile of a select population for a clinical trial. They may have comorbidities, it's not controlled, it's not under a proscribed set of instructions as to how to take the drug. So you have much more risk. The risk goes up because the proportion of patients taking the drug increases." -- pharma physician*

The informed consent document and process were mentioned by many participants as protecting the companies against allegations of research-related injury.

*From a doctor: "I would think, not being a lawyer, if in fact the consent forms were designed properly for clinical trials, and if the woman had a real opportunity to talk about the pros and cons of the disease, of the drug, and the possible outcomes, I would think litigation in the clinical trials might actually be less than in the post-marketing environment. Because in post-marketing, many people don't get the true, broad benefit/risk analysis of the drug before they start taking it." One of the lawyers agreed, "Historically,...it's hard for a plaintiff to succeed if there was informed consent."*

In spite of this, pharmaceutical company interviewees confirmed a real concern about the potential for litigation. They disclosed the litigation can result in high costs to the company, and damage to a company's reputation.

*"Obviously, pregnant women and children or babies are hot button emotional topics for juries and so it's not just, 'what is the risk of being sued?' but if you lose, 'how much is the risk for damages?'"*

-- pharma physician

One pharma physician in clinical development described society's reaction to birth defects by saying that *"squeamish is too benign a term. Apoplectic is more like it."* He went on to say that, *"A new chemical entity or an unregistered chemical entity would be an easy target."*

From a company lawyer:

*"Liability – this is an emotional, sensitive subject. I can see how in a lawsuit, any harm to a mom or a fetus could play well to a jury. There would be unknown damages, speaking objectively. Therefore, I would caution any sponsor in enrolling pregnant women especially in the absence of data that says it is safe or if it may not be effective – the potential harm would give us pause."*

In a similar vein, one of the participants referred to another company that has a strong reputation for conducting pregnancy registries for their products that are intended for use by women of childbearing potential. For one such product, the company had identified an increased risk for a certain birth defect. Subsequent to this finding, the company was the subject of television and internet advertisements encouraging women who had used the product to call the law firms in the ads. Her concern was that the lesson learned was that a company might be at higher risk for having done a study and found a correlation than if they had not done the study at all.

A pharma physician cautioned that a little knowledge can be a dangerous thing. It may not be unusual to find a random birth defect in a small sample of pregnant women.



"This," he says, could be "suggested as [having] prior knowledge" and could be used against the Company in litigation. Another respondent agreed,

*"there are just not enough pregnant women who are exposed until the medications are on the market. Some of these things can't be studied and can't be evaluated until they are on the market and then you are dealing with...a less controlled, and more real-world environment."*

-- pharma epidemiologist

Whether or not the risk of litigation is higher in the clinical or the post-marketing arenas, the fear of such litigation is real and may have other consequences. One respondent described its impact saying,

*"It's very tough. I can tell you that within major Pharma, there are drugs that can be very useful and that address a very clear unmet medical need that are being given thumbs down by senior management because of the specter of endless litigation."*

-- pharma physician

In the end, the advice of a company attorney was that, "I'm not sure either way that the litigation issues ought to drive you either to do or not to do trials [in pregnant women]."

Stated another, "you never know if you'll lessen the litigation risk, but you know, we accept litigation as the risk of doing business."

### **Key Findings for Section 2b.: Litigation Environment**

My perception was that this question had not been widely considered by the study participants. But the issue is raised in the literature: pregnant women are using marketed medication that has not been studied in pregnant women. The result of not testing the products on pregnant women in the controlled clinical trial environment is that pregnant

women take medication in the post-marketing environment usually without the benefit of informed consent, risk minimization considerations, and the enhanced monitoring of her pregnancy and the fetus that would be available in a study. Consider the difference in the number of birth defects that occurred when thalidomide was on the market (>10,000) compared to the number of defects that might have occurred in a clinical trial before the teratogenic effect was identified (I would estimate 3 or 4).

Key Finding #1: Pharmaceutical companies are concerned about litigation risks associated with testing products on pregnant women in both the clinical trial and the post-marketing environment.

Key Finding #2: Fear of litigation about birth defects may be deterring the development of potential pharmaceutical interventions that address unmet medical needs of the general population.

Key Finding #3: The risk of litigation is perceived to be higher in the post-marketing environment than in the clinical trial setting.

### **3. Reasons for Inclusion / Opportunities to Include**

After discussing the reasons that pregnant women are currently excluded from participating in clinical studies, the converse question was asked to ascertain if, despite understanding why they are excluded, they might also understand why they should be included?

**Aside from studies that are specifically about conditions of pregnancy, can you give me 3 or 4 reasons why a Company (or an IRB) should or might want to include pregnant women in clinical trials?**

Finding that the key informants could list many reasons why pregnant women should be included in clinical research, one can extrapolate that to suggest that there are many others within industry who feel the same way. The reasons they cited are summarized in Table 6.4.

**Table 6.4 Key informants' reasons for including pregnant women in clinical trials**

<b>Reasons to include pregnant women in clinical research</b>	
It's the right thing to do	When the benefit exceeds the risk
There is medical need	To aid the company reputation
To assist health care providers	To inform the product label
To fully evaluate the product's safety profile	To develop medicines that treat the population
To improve insurance coverage for medications	As a competitive advantage
To emulate best practices in other special populations like the elderly and pediatrics	

These reasons are very similar to those cited in the literature (see Literature Review, Chapter 2) with additional attention to the benefits that might accrue to the product and to the company.

Having established that people within industry and related organizations see the need for improved knowledge on how to treat medically compromised pregnancies, the next step was to ask for their input on how to do that. The participants in this study were very experienced in their respective areas and so would likely represent current thinking on the topic and/or could provide suggestions based on experience within their companies and organizations.

**"What would it take to have companies open (or IRBs approve) relevant clinical trials to pregnant women? Would a guidance document be strong enough or would it need to be by regulation?"**

*"I think it would take a woman CEO."* -- biotech physician

*"I think it would take a woman CEO. People who have had issues with (pregnancy), people who have wanted information and have had to make difficult decisions with the pregnancy are more conscious of these issues than people who haven't."*

-- biotech physician

*"I think it would require FDA to have a strong position. And then I think you'd need patient groups that would be pushing. And then I think you would need enlightened researchers in the company that are willing to take the next step for research in the 21st century. I think we still very far from it."*

-- biotech physician

A pharma industry lawyer reasoned that, because there is no regulatory impediment to the inclusion of pregnant women, there is no need for a guidance or regulation. However, most of the interviewees thought a guidance document would be an effective tool to get the dialogue started, to get stakeholders to take notice of the issue, to raise consciousness.

*"[A guidance] would be your first step to actually having sponsors not be fearful to include pregnant women in clinical trials. And it would be a huge step for the IRB." "It is the FDA standing up and saying, 'we support this.'"*

Respondents considered a guidance to be "*a favorable fact in litigation,*" and "*a sanction for enrollment.*" Without a guidance document, most thought that very little would happen. Said one IRB representative, "*...if they're not providing guidance, believe me, IRB's aren't going to want to touch it.*"

However, many felt that a guidance document would not be enough for companies to change their practice of excluding pregnant women from the drug development process.

*"Certainly a good, thoughtful guidance document would be helpful for the really altruistic company or one where this is the nuts and bolts of their indication to treat non-pregnant related illnesses that occur during pregnancy. But my guess is, unless told to do so, most companies would not."* -- pharma physician

*Another participant concurred, "The experience with studies in children suggests that a regulation would be necessary."* -- pharma physician

*Another agreed, "If we want a universal way of doing it, then I think there needs to be a regulation. Otherwise it will depend on the goodwill and the interests of companies and will be very uneven."* -- biotech physician

But not all were convinced that a regulation is the answer either.

*"From a litigation perspective, it would be a good defense. But I can't see them saying you have to do it - it would pose a risk for the FDA."* -- pharma lawyer

Study participants expressed hope that a regulation would not be required.

*"I personally have this philosophy of, 'don't give me a rule if I don't need a rule.' Or a law. And while I applaud the success that the pediatric laws have had driving people to the right space, I would just love to think that we could get this just by the force of public need without having to think about regulation. Goodness knows we've got enough of them as it is."* -- FDA representative

*"I also realize that these large business enterprises called pharmaceutical companies have so much going on that sometimes they don't pay attention unless there's a rule. I'd hate to think we have to go there. I really would love to see this take root without having to go much beyond guidance."* -- FDA representative

Others agreed that guidance documents, while non-binding, are difficult for companies to ignore, and, for the most part, *"companies conform."* With guidance

documents, said a PhRMA lawyer, "you get additional clarity that is quick and adaptable, easier. Regs are too vague, guidance can be more detailed." Another physician observed that guidance recommendations "can be achieved more easily and harmonized more easily" across institutions, states, and even across countries.

Additional follow-on questions were asked to solicit more specific information.

**"Would Company indemnification be necessary? Is that a realistic option?"**

*"...if you're not doing things properly, you're going to be sued, I don't care what the indemnification says."* -- pharma physician

Because the perceived risk of company liability was high among industry and IRB participants, the question of Company indemnification was explored. Most respondents did not think that Company indemnification was a realistic option.

*"I think there are instances where clearly things were not done properly and then indemnification doesn't matter to me anymore. Indemnification would not [persuade] me one way or the other. I'm not sure it really works in the final analysis because if you're not doing things properly, you're going to be sued, I don't care what the indemnification says."* -- pharma physician

But other participants, once prompted to think further about the possibility, voiced interest in its potential. An IRB representative was aware of current efforts by a governmental committee to explore this issue further.

*"There are people who are pushing for national funds to reimburse research injury. The Presidential Commission just recommended that in a recent report, following up on the Guatemala issue.<sup>‡</sup> Recommendations were: improved accountability and expanded treatment and support for research subjects injured in the course of [a study], because subjects harmed in the course of research should not bear the cost."*<sup>244</sup> -- IRB physician

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<sup>‡</sup>The "Guatemala issue" refers to a recently uncovered study conducted in 1946-48 by the U.S. Public Health Service involving the intentional exposure of subjects to sexually transmitted diseases without their consent.

He continued, "*they cite the national Vaccine Injury Compensation Program (VICP) as the example here.*" [The VICP was enacted in 1986 "to reduce the potential financial liability of vaccine makers due to vaccine injury claims. The legislation was aimed at ensuring a stable market supply, and to provide cost-effective arbitration for vaccine injury claims.]<sup>245</sup> Other participants disagreed with a parallel between the VICP and potential indemnification for studies with pregnant women, citing vaccines' more significant public health impact and the absence of a comparable market concern as differentiating factors.

*"Well, so a guidance document is interesting but probably would not be sufficient to overcome the other concerns that companies have. Carrots, like a patent extension, also may not be sufficient to overcome if there are serious litigation risks. So, indemnification might actually be important. So, for a society and a Congress that really wants to foster drug development [in this area], that might be the most effective way to do it. So you give a carrot [a patent extension] and a safety net for a specific list of conditions. This list of conditions should be studied and if there is a bad outcome for a pregnant woman enrolled in one of those studies there is indemnity for the company and a separate fund for recourse for the injured party. That might be good. You could look at vaccines as a model."*  
-- pharma physician

**"Would patent extensions, like those implemented for pediatric trials, be a viable enticement?"**

*"Be careful what you wish for."* – FDA representative

Many participants agreed patent extensions were a viable partial solution:

*"We pharmaceutical companies love patent extensions, because it takes a lot to get a drug on the market. I think it may be required,*

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<sup>244</sup> Presidential Commission for the Study of Bioethical Issues. (2012). Moral Science: Protecting Participants in Human Subjects Research. Washington, D.C., 2011. Retrieved from <http://www.bioethics.gov/cms/node/558>

<sup>245</sup> Wikipedia contributors. (n.d.). National Childhood Injury Act. In *Wikipedia, The Free Encyclopedia*. Retrieved April 1, 2012 from [http://en.wikipedia.org/wiki/National\\_Childhood\\_Vaccine\\_Injury\\_Act](http://en.wikipedia.org/wiki/National_Childhood_Vaccine_Injury_Act).

*because if you're going to take the risk of doing it, the patent extension may make it worth your while."* -- pharma physician  
*"Patent extensions have worked for pediatric exclusivity; it could possibly work in this particular case."* -- pharma physician  
*"A Company is taking extra risks that have monetary value."*  
-- pharma lawyer

Another suggestion extended the concept of patent extensions to include transferable extensions.

*"You could either extend the patents or you could have a certificate that allows you to transfer it to another product. So, there the statute says that [if] the manufacturer is developing a drug for a rare and, I think maybe, neglected disease drug and they get it approved, they can transfer the patent extension to another drug. So if you've got a multibillion-dollar drug and you are allowed to get an extension on that drug by developing a new orphan drug, that's a huge incentive. So, [either] extend the patent for the product for which it's developed or transfer the extension to another product."* -- biotech physician

However, others expressed dissatisfaction with their patent extension experience in the pediatric sector.

*"By the time you complete the pediatric program, get through all of the hoops and things, you still might turn out to be too late and you've lost patent already or they've taken so long that a patent extension doesn't add much. Or with the generic challenges to patents that come up so frequently, the patent extension may not be worth a hoot and holler... [I]t worked out in one of our cases, that we got the six-month patent extension followed one month later by a patent suit and the judge ruled in favor of the challenger."*  
-- PhRMA representative

The FDA participant also advised caution stating that, *"Patent extensions would be tightly linked to the expectation that we have a rule or a law. So if you go that route it means that you're conceding that we need some kind of regulation. Be careful what you wish for."*



However, there is a downside to patent extension in the public sector. *"Patent extensions are kind of unpopular among the general public these days,"* said an IRB representative. A pharma lawyer agreed:

*"the last thing that industry would want is to seem like they're doing this from a profit motive as opposed to a public health concern and certainly they've taken a fair amount of criticism for even the pediatric extensions despite a clearer benefit from a public health perspective. It's hard to think that would be that helpful."*

A lawyer at PhRMA also agreed, stating that,

*"Congress is likely not to grant any more patent extension approaches. I think there's a feeling now, with policymakers for some time now, that it hasn't been a great solution. ...there have been some perceived cases that... were seen as industry trying to get the extra market exclusivity ...you will get some backlash." And finally, one participant observed that, "the current fiscal environment is at odds with providing additional exclusivity."*

To open the issue up to the study participants to contribute additional thoughts or ideas on the topic, the open-ended question was asked: **"Are there other solutions or incentives you can think of?"**

*"Just put a whole package of things out there and let them react to it."*  
-- biotech physician

When asked this question, the interviewees responded with a myriad of ideas, commentary, and topics for further discussion. Many concluded their comments with a pessimistic appraisal such as, '...but I don't think that will work.' I have organized these ideas in the table below under targeted headings.

**Table 6.5 Participants' observations, suggestions, and potential solutions**

Observations and Recommendations from Participants	Solutions
<b>On the Business</b>	
The company...has to adopt it from a very high level. It's got a come down from the top, that the company understands the problem and is willing to commit the company resources to doing it. It's got to take upper management to require it - I don't think the clinical monitors are going to embrace it.	<b>Establish commitment at the top</b>
My hope is that the guidance would at least drive the companies back to reviewing their current feelings on this.	<b>Respond to FDA guidance</b>
I have this vision of, once we get over the hump of the concerns - which we've done before, first with women, then with kids, now with pregnant women – it should just be part of the normal [drug] development scheme.	<b>Make routine part of drug development</b>
[Companies] have to see that there's good public relations, that it's good for the company, good for the industry, good for the sector.	<b>Public Relations Opportunity</b>
They'd have to see more companies doing these trials...they have to see success in these trials and then I think they would be more interested in perhaps doing it. You'd want benchmarking - the Company would want to be in the middle of that bell-shaped curve. Maybe once some Companies start doing it and it doesn't result in negative outcomes, more companies might start doing it. I don't think there are enough upsides. There's more downside risk than upside benefits.	<b>Benchmark practices and successes</b>
You face the obstacle of businesspeople without that [scientific] knowledge base. If they would look to their scientific colleagues - but they're looking at the business from an entirely different perspective.	<b>Have science drive the decision</b>
In pediatrics, there's a market; with pregnant women,...not very much. So from a commercial perspective, it is completely unappealing for the Company.	<b>Define the market</b>
<b>On Litigation</b>	
I think if they knew the data well enough and knew that the drug could help those women without severe consequences to the company, without risk to the company, I think they wouldn't get in the way, they wouldn't prevent it from being done.	<b>Legal community advisement in assessing real risks and devising protections</b>
I think if ...there was some liability for <i>not</i> treating the woman when you could save her life or spare her from increased morbidity, I think that might persuade them as well.	
<b>On FDA</b>	
...more data can potentially get you a better pregnancy category. [I]f the company does do studies in pregnant women and that [information] could be then included in the label, that might be yet another incentive. Some drugs are thought to be better for you in the pregnant population. That being based on real scientific data might be an incentive.	<b>Implement the Pregnancy Labeling Rule</b>
FDA needs to have...more pats on the back, it needs to do some things that will, you know, [give them] 'Atta Boys.' Once they start thinking outside the box with some of these things, they're going to be in the same position they've been [in] which is kind of the whipping dog of Congress and every other group that wants to criticize them for stuff.	<b>Strengthen public advocacy for FDA's efforts</b>

And there should be a bit of a, "if you don't do this, especially if the drug or vaccine has a high likelihood of being used by pregnant women, this may be harsh but, it may jeopardize your indication or authorization." We had something very similar. [FDA] said if you don't do this elderly study, you are not going to get an authorization and now we're doing an elderly study. We never would have done it unless they said that in writing.	<b>Implement sanctions for not doing studies</b>
Every month the drug's not approved you lose a lot of money, so early approval is really an incentive as well. I think what [companies] really want is rapid processing of their applications so that it gets reviewed and the FDA makes the decision.	<b>Implement fast track review as incentive</b>
I'm not sure there's enough dialogue that takes place between pharmaceutical companies and regulatory agencies throughout drug development. I think these issues need to be discussed early and they need to get some real strong guidelines from the regulatory agency. These agencies have a lot of power and pharmaceutical companies really have to listen to them to get the drug approved. Part of the problem too, is when you try to make an appointment to see some of the people in the regulatory agency, they don't have the time and they push back. And I think you really have to be able to talk with them so that you know what they're thinking and they know what you're thinking.	<b>Release the new guidance document; Improve access to dialogue between FDA and Sponsors</b>
I do think however that some sort of financial break has to be taken into consideration. Our pediatric studies are extremely expensive, high risk, and you may or may not gain any financial benefit from it, which is OK in a way, but then a generic company comes along a month later and benefits...	<b>Provide some financial incentive to Sponsors of studies</b>
<b>On Advocacy</b>	
I think it needs to be on the agenda of PhRMA and Bio. It takes having a number of position papers out there, white papers, symposia, soliciting interest from professional groups, ACOG, AAP, and other groups. It really takes a concerted effort so that they can all write supportive statements and documentation. The point is that it gets into the collective consciousness.	<b>Involve professional, industry, and medical groups</b>
It comes back to advocacy. You need a think tank to be behind you in this, you need a Washington think tank. The Second Wave coalition might be the group you need so that they can develop position papers, they can be in contact with the different stakeholders. You have to get stakeholders onboard. And you have to be in this for the long haul, this is not a one-off. ...So you really need to be developing those discussions now in order to have any chance of getting on the [PDUFA] agenda for 2017.	<b>Sustained work by central advocacy group; develop position; involve stakeholders</b>
For policy advocacy, use anecdotes. They work. The anthrax example is a good one.	<b>Use anecdotes for advocacy</b>
Starting off with the regulation or guidance, if they're having groups of experts or an advisory committee to the federal government; if you have more and more respected academics, clinicians proposing why it's important to include pregnant women in clinical trials; if you get all of those things out there; use professional organizations proposing guidelines, anything like that, that's going to help pave the way. Or maybe even include pregnant women...; the more and more support you have for that, the more and more it can catch on and you'll get an okay to include them for various conditions.	<b>Involve stakeholders: academics, clinicians, pregnant women; professional organizations</b>
[This is] going to take a whole lot of work on the outside of getting folks together in those spaces where we all gather professionally, that have these	<b>Bring stakeholders</b>

debates around what's needed and how the best to do it. Not under the shadow of impending law. So that was my idealist speech. I don't think that will happen but it would be nice.	<b>together in public forums</b>
I think historically pregnant women are classed in....the category of vulnerable patient populations and to the extent that there's a push to say, we're not vulnerable, in fact, we're patients who need to understand the implications of taking different treatments. It's almost like a cultural change rather than a regulatory change.	<b>Remove the vulnerable population label from pregnant women</b>
I don't think that you will have a lobby of pregnant women because it's different [than pediatrics].	<b>Lobby</b>
Is the pregnant population as compelling as the pediatric population? I think the perception is that the pediatric population is more underserved.	<b>Advocate for pregnant women's needs</b>
This is where I think the change is going to come - when companies are consistently asked what their position is. And that could be by the agencies, by the IRB's, could be by the public. They're going to have to hear multiple voices, but particularly IRBs and FDA.	<b>Have companies clarify their position</b>
I think what would help if [there was] more talk about this ethic. If you could get patient groups talking about it, get onto TV, and if people, if it became an actual issue that society cared about. I feel as though it isn't at the moment.	<b>Involve patient groups, advocate in public arena</b>
Is there a quantitative assessment that could be done? If pregnant women were not protected [from anthrax], what was that cost? Compare mortality and health costs with the risk of birth defects.	<b>Quantify the cost of exclusion</b>
<b>On Stakeholders</b>	
Personally I'd like to see partnerships between a group like the NIH, industry and maybe even third-party payers, to supporting this effort.	<b>Build Partnerships</b>
Mitigate the risk by building better relationships and partnerships for a trial.	
One would hope that the first company that's going to be really brave to come in and say, 'we want to do this,' will come in...to speak to NIH or FDA or whoever, and say, 'here's the trial we want to lay out,' and [they] will not [be hearing] of this for the first time. And they'll be willing to work with each other to make it happen.	
So to some degree I think the financial responsibility of undertaking.... things which may be largely of public health interest and not necessarily the pharmaceutical interest, but to support public health interest and science, should really be shared more broadly by a wider group of people. Not necessarily government but maybe the generic companies, public health groups, NIH and those sorts of organizations.	<b>Share responsibility for public health</b>

In summary, participants in the study suggested that increasing the inclusion of pregnant women in clinical studies is such a difficult and controversial undertaking that any and all suggestions for how to make it happen should be on the table for consideration.

### **Key Findings to Section 3. Reasons for their Inclusion / Opportunities to Include**

Key Finding #1. Most of the participants believe that a guidance document from FDA on the topic of including pregnant women in clinical trials will increase awareness and discussion within and outside of the pharmaceutical companies, but that it may not be enough to cause a change in current practices.

Key finding #2. Company indemnification should be included when considering all the potential solutions to improving knowledge of pharmaceutical therapy for pregnant women.

Key finding #3. Patent extensions and transferable extensions should be considered cautiously due to negative industry and public perception.

Key finding #4. Stakeholders within and external to the pharmaceutical industry have suggestions on how to improve the inclusion of pregnant women in clinical research.

### **C. ETHICAL CONSIDERATIONS**

One of the challenges in doing research with pregnant women is addressing the ethical issues it raises. The study participants were asked,

**What ethical problems do you think are most challenging or important?**

*"You've got disenfranchised women basically. They're truly disenfranchised."* -- biotech physician

In response, they expressed a number of concerns regarding the ethical issues raised by the subject matter. Traditional medical ethics – non-maleficence, justice, and autonomy – were raised, along with a suggestion that perhaps feminist ethics could make a contribution to the debate. They struggled with issues like society's uneasy relationship with fetal protection, abortion, informed consent, and the difficulties in considering and balancing both maternal and fetal benefits and risks. Some passionately described their feelings about the dichotomy inherent in the pharmaceutical industry's mission. Does the company's responsibility to provide medical products to improve the health of the population supercede or follow the corporation's mandate to at least remain solvent or, preferably, generate and increase profit?

While most participants felt that pharmaceutical companies had an ethical responsibility to obtain safety and efficacy information for products that would be used by pregnant women, many acknowledged that business considerations might be the deciding factors in whether such research would be conducted. The attitude of senior management and regulatory agency guidance were recognized as factors that could influence such decisions.

#### **D. CONCLUSION**

The participants in this qualitative study provided insightful, thought-provoking, and sensitive responses to the issue of the inclusion of pregnant women in clinical research. Having joined the pharmaceutical industry, an IRB, or the FDA in order to help humanity by assisting in efforts to prevent, treat, or eradicate disease, these key informants grasped the implications of treating pregnant women with interventions that have not been tested on pregnant women. And they grappled with potential solutions to address the problem.

There were 55 key findings generated by the interviews with key informants (see Appendix IV. Qualitative Study Results). Of these, several deserve attention as indicators of the strength of the current status and as measures of the potential for change.

1. The pharmaceutical industry has excluded pregnant women from participating in clinical research based primarily on the ethical principle of beneficence. The sincere perception, in keeping with the perceived attitude of the general public, is that the inclusion of pregnant women in the study of developmental drugs is too risky for the fetus and that exclusion is the safest approach.

2. The adverse consequences of pregnant women's absence from research are largely unrecognized by the industry. They are also unaware of stakeholders' desires to increase their inclusion, and the impending release of the FDA draft guidance on this subject.

3. Individuals within pharmaceutical companies and IRBs, when engaged in dialogue on this issue, recognize the attendant, though unintended, adverse consequences of pregnant women's exclusion from clinical research and agree with the need to change current practice.

4. Experienced researchers within the pharmaceutical companies – experts on clinical trial design and conduct – can readily provide practical solutions to overcome the perceived barriers to pregnant women's inclusion in clinical research studies.

5. Pharmaceutical company researchers and lawyers, and colleagues in associated organizations like IRBs and trade associations, think that change to the current practice of excluding pregnant women from clinical research studies will be difficult to implement. They believe that, aside from safety issues, valid business concerns must be recognized and addressed before change will be considered. These include: the additional time and financial

costs with little return on investment, potential delays and threats to product approval, litigation risks – both financial and reputational, and challenges in study design and validity. Therefore, change to current practice, if initiated, will likely be incremental.

6. Inducing change in the well-entrenched practice of excluding pregnant women from clinical research studies will require regulatory directives, financial incentives, and legal protections.

Table 6.6 summarizes some of the most common concerns the participants raised with some of the potential solutions they suggested to address the issues.

**Table 6.6 Barriers and solutions identified by key informants**

<b>Key Concerns / Barriers</b>	<b>Key Potential Solutions</b>
Causing harm to the fetus	Study design, scientific advances in modeling and animal testing
Litigation	Standardized study design, guidance/regulation, improved awareness of issue in public domain
Scientific concerns	Initiate study after animal testing and general population results, PK testing, data from inadvertent exposures and post-marketing surveillance
Negative impact on initial approval	Post-approval studies
Lack of regulatory agency support	FDA Guidance document, international harmonization
Unclear regulations	FDA Guidance document, international harmonization
Potential negative reputational impact	Data interpretation standardization, FDA guidance; improved awareness of issue in public domain
Lack of advocacy from stakeholders	Increase awareness of issue
Lack of experience and know-how	Collaboration, innovation, science



## Chapter 7

# The Plan for Change

### A. Conceptual Framework

In 1995, John Kingdon proposed a "Policy Window" theory of change in his book, *Agendas, Alternatives, and Public Policies*.<sup>246</sup> In it, he identified three relatively independent issue workstreams whose interactions are required to advance social change. Kingdon called the participants in the workstreams "policy entrepreneurs," people who are "willing to invest their resources in return for future policies they favor."

The three issue "streams," Problem (recognition), Policy (proposals), and Political (influence), can move along independently until a point in time when they "converge," often due to external forces. This convergence allows the issue and its potential solutions to be recognized across parties. The "window of opportunity," if capitalized on by the entrepreneurs, can put the issue on the political agenda for resolution by the parties involved. The result is the advancement of social policy.

Entrepreneurs in the problem recognition stream identify, describe, and frame an issue as a problem when it may not have been recognized as such before. Problem

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<sup>246</sup>Kingdon, J. (1995). *Agendas, Alternatives, and Public Policies*, 2<sup>nd</sup> ed. New York: Harper Collins College.

definitions often have an emotional values component which helps them to get on the agenda for change.

Entrepreneurs in the policy stream contribute potential solutions to a "primeval soup" in which "ideas confront, compete, and combine with each other" and eventually result in policy formulation.<sup>247</sup> The process relies on groups of interested and knowledgeable parties to propose multiple solutions that are both "technically feasible and consistent with policymaker and public values."<sup>248</sup> These policy entrepreneurs "must possess knowledge, time, relationships, and good reputations."<sup>249</sup>

The political stream is critical to getting the issue on the agenda for solution. The policy entrepreneur "recognizes the problem, attaches an appropriate policy proposal to it, and floats the policy proposal in various forums"<sup>250</sup> to bring it to the attention of the people with the power to place it on the agenda for change. Political events may occur unrelated to the issue at hand. Astute policy entrepreneurs can recognize the relationships among the event, the problem, and its proposed solutions and connect the streams. The result of the

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<sup>247</sup>Lieberman, J.M. (2002). Three streams and four policy entrepreneurs converge: A policy window opens. *Education and Urban Society*, 34(4), 445.

<sup>248</sup>Stachowiak, S. (2009). Pathways for change: Theories about how policy change happens. *Organizational Research Services*. Retrieved from [http://www.organizationalresearch.com/publications\\_and\\_resources\\_featured.aspx](http://www.organizationalresearch.com/publications_and_resources_featured.aspx)

<sup>249</sup>Stachowiak, S. (2009). Pathways for change: Theories about how policy change happens. *Organizational Research Services*. Retrieved from [http://www.organizationalresearch.com/publications\\_and\\_resources\\_featured.aspx](http://www.organizationalresearch.com/publications_and_resources_featured.aspx)

<sup>250</sup>Lieberman, J.M. (2002). Three streams and four policy entrepreneurs converge: A policy window opens. *Education and Urban Society*, 34(4), 445.

convergence of two or three of the streams is that "a compelling problem is linked to a plausible solution that meets the test of political feasibility."<sup>251</sup>

Kingdon's Policy Window theory of change is most useful when "capacity exists to act on policy windows."<sup>252</sup> He recommended special studies of the social issue to 1) provide indicators of the existence and magnitude of the issue and to 2) promote constituent feedback. This study used quantitative methodology to provide such indicators and qualitative methodology to collect such feedback. The next step was to bring these study findings to the policy window that I believe is about to open to facilitate a correction in the lack of reliable information about the safety and efficacy of the medications we use to treat medically compromised pregnancies.

## **B. Application of the Study Results to a Plan for Change**

### **1. PROBLEM STREAM**

This study sought to isolate the perceptions of the pharmaceutical industry about the barriers to and opportunities for a broader inclusion of pregnant women in clinical research. In a 2010 conference on maternal and pediatric drug safety, a speaker suggested that it was time for the industry to be brought into dialogue on this issue. The role and perceptions of industry had been identified as a gap in knowledge among advocates. As an industry

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<sup>251</sup>Boussagué, L., Jacquot, S., & Revinet, P. (2004). *Dictionnaire des Politiques Publiques*, Presses de la Fondation Nationale des Science Politiques, p. 217-225. Retrieved Oct. 12, 2011 from [www.metagora.org/training/encyclopedia/Kingdon.html](http://www.metagora.org/training/encyclopedia/Kingdon.html)

<sup>252</sup>Stachowiak, S. (2009). Pathways for change: Theories about how policy change happens. *Organizational Research Services*. Retrieved from [http://www.organizationalresearch.com/publications\\_and\\_resources\\_featured.aspx](http://www.organizationalresearch.com/publications_and_resources_featured.aspx)

"insider," I felt uniquely well-positioned to initiate a conversation from within. The focus of my study and my Plan for Change are change within the pharmaceutical industry.

In 2000, a multidisciplinary conference was convened by the University of Texas Medical Branch to "address the national problem of underrepresentation of pregnant women in clinical trials." In 2009, the Second Wave Consortium held an invitation-only workshop to address the issue. Despite being one of the major stakeholders in the design and conduct of clinical trials, no one from the pharmaceutical industry was in attendance at either forum. This study found that pharmaceutical company employees, IRB members, and PhRMA representatives were unaware that the exclusion of pregnant women from clinical research was perceived to be a problem. Study participants believed that they were doing the right thing by not including pregnant women in clinical trials based on the ethical injunction to "do no harm."

Kingdon found that "problems...are matters of interpretation and social definition"<sup>253</sup> and that issues are only perceived to be problems when there is pressure to do something about them.<sup>254</sup> It was clear from my interviews that no one in industry was working on a solution to this problem because they had not perceived it to be a problem in the first place. Nor did they feel any pressure from external stakeholders – health care providers, pregnant women, professional groups, or support organizations – to address the issue. *"There's just been no interest in looking at this..."* stated one study participant. *"Who's really advocated*

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<sup>253</sup> Rochefort, D. A., & Cobb, R. W. (1993). Problem Definition, Agenda Access, and Policy Choice. *Policy Studies Journal*, 21(1), 57.

<sup>254</sup> Reddington, L. (2009). The Orphan Drug Act of 1983: A case study of issue framing and the failure to effect policy change from 1990-1994. (Unpublished doctoral dissertation). University of North Carolina, Chapel Hill, NC, p. 14.

*for clinical trials in pregnant women?"* The key informants suggested that the lack of interest from within and outside of the companies provided little incentive to initiate change.

However, during the course of the interviews, all of the participants expressed an understanding of the potential problems associated with the exclusion of pregnant women from research studies and they were able to suggest potential solutions. I found that the anthrax/amoxicillin PK study provided a "persuasive and compelling" problem illustration and it was all that was needed to shift the perception from exclusion being a normal and ethical practice to it being a practice in need of re-evaluation in light of its potential harms. These key informants did not think that change would be easy (one referred to the "*seachange that we have to have here,*" another suggested that the general public is "*apoplectic*" about issues involving the fetus), but they did see the need for further thought on the topic. This study's results identified the need for broader problem recognition among the stakeholders.

Very few key informants had heard of the Second Wave Consortium. Likewise, very few were aware that FDA had a guidance document (Pregnant Women and Clinical Trials: Scientific and Ethical Considerations) on the 2011 docket for development. Obviously, this lack of awareness precluded work on a solution.

The study also found that the industry is perceived to be a powerful decision-maker in control of the inclusion and exclusion parameters of a clinical trial. While the FDA, the IRBs, and the institutions at which the research is conducted were all perceived to have "veto power" – that is, they could reject a study protocol proposed by the industry – participants agreed that they had little power to demand that pregnant women be included if the company

was not in favor. Therefore, targeted advocacy to industry will be important to change the current status.

These findings suggest that improved awareness of the problem is needed both within and outside of the pharmaceutical industry. To ensure focus and feasibility, this dissertation and plan for change is targeted to industry. But the work of advocacy groups is recognized as being essential to the effort to broaden the inclusion of pregnant women in clinical research. See White Paper (Appendix VI) for suggestions from the study for advocacy groups external to industry. In addition, I intend to share the results of this study – a copy of the dissertation and the White Paper – with advocates in the Second Wave Coalition.

**a. The Plan for Change in the Problem Stream:**

The release of the FDA guidance document will provide the impetus to move from little or no internal discussion of the issue to dialogue and collaboration across industry. Once the document is released, industry will have to respond. The release of the document will be the opening of the policy window. Therefore, advocates will need to lay the ground work now and get ready to move when the document is released into the public domain with a 60 to 90-day period for public comment.

I was advised by one of the key informants that

*"It takes having a number of position papers out there, white papers, symposia, soliciting interest from professional groups, ACOG, AAP, and other groups. It really takes a concerted effort... The point is that it gets into the collective consciousness. At the moment there is nothing." He continued, And you have to be in this for the long haul..."*

Kingdon agreed. "Of all the attributes of successful policy entrepreneurs that I could name, sheer persistence is probably the most important."<sup>255</sup>

**Table 7.1 Plan for Change in the Problem Stream: Understanding the Problem\***

<b>Plan #</b>	<b>Goal</b>	<b>Target</b>	<b>Intervention</b>
<b>1</b>	Increase <b>awareness of the current practice</b> of including pregnant women in, or excluding them from, clinical research	Industry, Stakeholders, General Public	Published paper on extent of exclusion in scientific literature
<b>2</b>	Increase <b>awareness of the 'issue as a problem'</b> among individuals in industry, IRBs, and industry associations	Industry colleagues, Senior management	White Paper <sup>†</sup> to key informants, PhRMA and BIO; Conference presentations

\*See Complete Plan for Change in Appendix V.

<sup>†</sup> See White Paper in Appendix VI.

### **Plan for Change Proposals**

**a.** Increase awareness of the current practice of including pregnant women in, or excluding them from clinical research

**Goal:** Raise awareness and add to the public knowledge base. The current practice of including or excluding pregnant women from clinical research is not quantified in the literature. Results of the quantitative study will make the current practice explicit to improve understanding of the extent of current practice. It will also provide a benchmark against which to measure change.

**Target:** Industry stakeholders, General Public, Academia

**Intervention:** I will submit a paper using the findings of the quantitative analysis of clinical trials for publication in a professional journal. (See Chapter 5. Quantitative Results

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<sup>255</sup>Kingdon, J. (2005). The reality of public policy making. Chapter 6. In Danis, M., Clancy, C., & Churchill, H.R. Ethical Dimensions of Health Policy. New York: Oxford University Press, p. 101.

which is a draft of the paper.) The paper will not only share information to initiate discussion, it will also provide a baseline against which to evaluate the impact of efforts to improve the inclusion of pregnant women in clinical trials. The finding that only 6% of Phase IV studies currently include pregnant women will provide a baseline to benchmark against.

**b.** Increase awareness of 'the issue as a problem' among individuals within the pharmaceutical industry, the IRBs, and the industry associations.

**Goal:** To facilitate potential change, raise awareness among industry researchers and associated key stakeholders involved in the issue.

**Target:** Company employees and senior leaders, industry associations (PhRMA and BIO), IRBs. Company employees participate in dialogue and strategy sessions and influence company positions. These are the subject matter experts on whom senior leaders rely for information, issue evaluation, and problem solutions. At the same time, target senior management; these are the decision-makers and the allocators of the funding required to conduct research. One key informant stated, *"The company has to adopt it from a very high level. It's got to come down from the top, that the company understands the problem and is willing to commit the company resources to doing it."*

**Interventions:**

1) To facilitate laying the groundwork, I will submit a white paper to PhRMA and BIO, the pharmaceutical and biotechnology industry organizations, articulating the problem and sharing the results of the qualitative study.

A White Paper is an authoritative report or guide that helps solve a problem. White papers are used to educate readers and help people make decisions, and are often requested and used in politics, policy, business,



and technical fields. Policy makers frequently request white papers from universities or academic personnel to assist policy developers with expert opinions or relevant research.<sup>256</sup>

My intent is to provide industry with a better understanding of the issue, a prelude to what the FDA draft guidelines will likely contain, and – based on the results of this study – a set of potential solutions to a problem they have not, as yet, recognized but to which they will have to respond quickly following the release of the FDA guidance.

2) A second target for the White Paper are the key informants who participated in this study. Many expressed interest in learning of my results and are well-positioned within their respective companies and organizations to initiate a dialogue with others there. My suggestion will be that they share it within their company in anticipation of the release of the FDA guidance. This process will reach four pharmaceutical companies and one Clinical Research Organization, three biotech companies, and three people within independent IRBs.

3) Finally, I am prepared to speak on this topic at industry and clinical conferences and workshops. Because of my longtime work on pregnancy registries, I am recognized as a subject matter expert and have published and presented widely on the topic of drug safety in pregnancy. I was recently invited to speak at the World Drug Safety conference in London in September 2012 at which I am prepared to speak on this issue. I will seek other opportunities to present on the topic in the U.S.

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<sup>256</sup>Wikipedia contributors. (n.d.). White Paper. In *Wikipedia, The Free Encyclopedia*. Retrieved July 15, 2011 from [http://en.wikipedia.org/wiki/White\\_Paper](http://en.wikipedia.org/wiki/White_Paper)

## **b. Public Health in the Problem Stream**

When I tell people that my dissertation topic is on the subject of including pregnant women in clinical trials, the usual and immediate response is, "you can't do that." People associate pregnant women and medication with thalidomide. I have found it to be a challenge to explain the issue in a way that allows them to see the benefits as well as the risks of participation in research. In addition, protection of the fetus is a prominent and sometimes volatile issue in current U.S. society. Even the 2000 conference on the issue stated that "the topic is controversial" and limited participants to invited guests because of what they termed, the "perceived sensitive nature of the topic."

The APHA Legislative Advocacy Handbook states that public health advocates should "use data and the public health human interest stories that you encounter in your workplace to further your advocacy efforts."<sup>257</sup> One key informant advised me, "*For policy advocacy, use anecdotes. They work. The anthrax example is a good one.*" Public health advocates have learned to use experience and imagery to communicate facts in a way that captures the audience's imagination and helps the message to stick in the recipients' mind. In 'framing an issue,' advocates "select some aspects of a perceived reality and make them more salient in a communicating text, in such a way as to promote a particular problem definition, causal interpretation, moral evaluation, and/or treatment recommendation for the item

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<sup>257</sup> American Public Health Association. (n.d.). APHA legislative advocacy handbook: A guide for effective public health advocacy. Washington, DC: Author. Retrieved March 24, 2012 from <http://www.apha.org/NR/rdonlyres/256C8E98-AC70-4CD0-87BA-6EDC048DB0E8/0/RulesandGuidelinesPHAdvocates.pdf>

described.”<sup>258</sup> Communicating about and supporting the position of increasing the number of pregnant women in clinical research can be a challenge.

To address that challenge, I found the anthrax treatment example to be helpful in conveying the seriousness of the lack of evidence-based treatment guidelines. In the examples below, bioterrorism, death, and abortion provide context for the consequences of underrepresentation of pregnant women in research. The use of such frames can assist advocacy efforts during periods of policy change.

- At the time of the anthrax scare in 2002, 500 mg amoxicillin three times a day for 60 days was a recommended treatment for anthrax-exposed pregnant women.

Subsequent study, published in 2007, revealed that this dosage and frequency would be ineffective against anthrax due to the effects of pregnancy on the pharmacokinetics of amoxicillin. The 2007 study recommended "further research...to determine appropriate antibiotic regimens for pregnant women in response to a bioterrorism attack."<sup>259</sup>

- In my work on a pharmaceutical company pregnancy registry, an obstetrician reported that a pregnant woman, concerned about the effect that drugs might have on her developing fetus, made the decision to stop using her asthma medications. When she was 7 months pregnant, she experienced an acute asthmatic episode and died.
- Pregnant women reporting to the pregnancy registry have told me that they have been advised by their doctors to terminate their pregnancies due to their inadvertent

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<sup>258</sup>Entman, R.M. (1993). Framing: Toward clarification of a fractured paradigm. *Journal of Communication*, 43(4), 52.

<sup>259</sup>Andrew, M.A., Easterling, T.R., Carr, D.B., Shen, D. Buchanan, M., Rutherford, T., Bennet, R., Vicini, P., & Hebert, M.F. (2007) Amoxicillin pharmacokinetics in pregnant women: Modeling and simulations of dosage strategies. *Clinical Pharmacology & Therapeutics*, 81(4), 547-556.

exposure to drugs and vaccines during pregnancy. Whether the advice was given to protect the physician or the pregnant women was not determined.

- In addition to using anecdotes to illustrate issues, Dorfman et al., in their paper on Framing Public Health Advocacy to Change Corporate Practices,<sup>260</sup> recommend articulating "core messages that correspond to shared values." They cite Daniel Beauchamp's 1976 recommendation to frame issues using the public health core value of social justice.<sup>261</sup> The values of social justice include shared responsibility, interconnection and cooperation, strong obligation to the collective good, assurance of basic benefits, government involvement, and community superceding individual well-being. I think these values may particularly resonate with individuals in the pharmaceutical industry, many of whom have a background in medicine, nursing, pharmacy, and basic sciences - disciplines that promote the discovery and application of interventions that improve the public health.

Examples of messaging using core values of public health and social justice:

- It was the tragic outcomes from the use of thalidomide by pregnant women that triggered the 1962 FDA amendments that require efficacy and safety information be obtained from clinical trials prior to drug approval. It is especially ironic then, that pregnant women remain systematically excluded from the benefits of inclusion in clinical trials.

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<sup>260</sup>Dorfman, L., Wallack, L., & Woodruff, K. (2005). More than a message: Framing public health advocacy to change corporate practices. *Health Education and Behavior*, 32(3), 320-336.

<sup>261</sup>Beauchamp, D.E. (1976). Public health as social justice. *Inquiry*, 13, 101-109.

- Pregnant women are the last of the vulnerable populations to be included in clinical trials. More children, elderly, and inmates benefit from inclusion in clinical trials than pregnant women.
- It is doubtful that Millenium Development Goal #5 – Reduce Maternal Mortality – will be met. This is true in the developing world *and* in the U.S. where more than two women die every day from pregnancy-related causes<sup>262</sup> and more than a third of the 1.7 million women who give birth each year experience some type of adverse complication.<sup>263</sup>

In addition to clinicians and scientists, the pharmaceutical industry, one of the most profitable industries in the world, is also composed of business people. "The biggest barrier to achieving social justice," state Dorfman et al, "is the competing ethic of market justice." The business concerns of the industry were cited by the key informants in this study as powerful justifications to continuing to exclude pregnant women from participation in clinical trials.

Former U.S. Surgeon General Antonia Novello said that "one of the fundamental paradoxes of market oriented societies is that some entrepreneurs—even acting completely within the prescribed rules of business practice—will come into conflict with public health goals." That reflects the issue here; there is no mandate or requirement to broaden the

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<sup>262</sup> Heron, M., Hoyert, D.L., Murphy, S.L., Xu, J., Kochanek, K.D., & Tejada-Vera, B. (2009). Deaths: Final data for 2006, National Vital Statistics Reports, 57(14), I-136, p. 116. Retrieved from [http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57\\_14.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf)

<sup>263</sup> Daniel, I., Berg, C., Johnson, C.H., & Atrash, H. (2003). Magnitude of maternal morbidity during labor and delivery: United States, 1993-1997. *American Journal of Public Health*, 93(4), 631-634.

inclusion of pregnant women – it is simply the right thing to do. Therefore, framing the problem from a public health perspective (showing the values behind the reason for change) and using anecdotes to illustrate the issue at a fundamental level (making it personal) can move the dialogue toward collective solutions rather than entrenched positions. According to Kingdon, language, word choice and symbols are important and are used to promote selected interpretations, mobilize support, and influence the political environment.<sup>264</sup>

### **c. Public Health Leadership in the Problem Stream**

In "Building the Next Generation of Leaders," Joy Phumaphi, former Botswana Minister of Health says, "A leader who tries to drive the health agenda alone lacks vision. Every stakeholder needs to feel a part of the solution. To reach this point, all must see the problem."<sup>265</sup>

This study was done with the intention of bringing a key stakeholder, the pharmaceutical industry, into the dialogue on the inclusion of pregnant women in clinical research. My research showed that the industry was not aware of the problem, in fact, their perception was that the exclusion of pregnant women from clinical research was the ethical position and the right thing to do. This research alerts industry stakeholders to the unintended consequence of this behavior in an effort to help them "see the problem" – and then work on solutions.

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<sup>264</sup>Reddington, L. (2009). The Orphan Drug Act of 1983: A case study of issue framing and the failure to effect policy change from 1990-1994. (Unpublished doctoral dissertation). University of North Carolina, Chapel Hill, NC, p. 14.

<sup>265</sup> Phumaphi, J. (2005). Building the next generation of leaders. In Foege, W.H., Global Health Leadership and Management, San Francisco, CA: Jossey-Bass, p. 190.

Martin McKee, professor of public health at the London School of Hygiene and Tropical Medicine, states that "Effective public health leaders should not simply wait to be asked for their opinion. They should be advocates for health, drawing attention to issues that would otherwise be overlooked." He continues that, because "public health is based on social justice, ...its advocates will often espouse causes that are unpopular."<sup>266</sup> I can confirm that advocating for the inclusion of pregnant women in clinical studies is not a popular stance to take within pharmaceutical companies. However, as a public health leader, I can call upon aspects of leadership that come from my experiential knowledge of this issue as a clinician who has treated pregnant women and as a researcher who has gathered data in pregnancy registries to inform treatment decision-making for pregnant women for many years. My position, which was confirmed by the key informants in this study, is that industry can "evolve" in the manner in which it considers and addresses the needs of pregnant women and their health care providers.

Advocacy calls upon non-traditional leadership models to promote change. Advocates often use 'Transformational Leadership' skills, leading with passion, inspiration and relationships<sup>267</sup> rather than authoritative leadership practices that are derived from positions of power. Advocacy leaders rely upon strong interpersonal skills to explore issues and communication skills to add stakeholder voices to the advocacy and problem solving

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<sup>266</sup>McKee, M. (2005). Challenges to health in Easter Europe and the former Soviet Union: A decade of experience. In Foege, W.H., Global Health Leadership and Management, San Francisco, CA: Jossey-Bass, p. 181.

<sup>267</sup>London, M. (2008). Leadership and advocacy: Dual roles for corporate social responsibility and social entrepreneurship. *Organizational Dynamics*, 37(4), 313-326.

process.<sup>268</sup> In the process of this study, I employed interpersonal relationships and networking skills to contact and dialogue with key informants. Communication skills and connections to influential personnel within the industry, will help me relay my findings in various formats and venues to influence key opinion leaders as outlined in this Plan for Change. In "Creating the Future of Public Health: Values, Vision, and Leadership,"<sup>269</sup> Barry S. Levy advises us to call upon "the values that brought you to public health in the first place and not be afraid to articulate them...with passion, with courage, and with persistence."

## 2. POLICY STREAM

In this study, the central 'policy' is the proposed FDA Guidance: Pregnant Women in Clinical Trials: Scientific and Ethical Considerations. Guidance documents, according to FDA,<sup>270</sup>

"...represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations." FDA describes the guidance review process.<sup>271</sup>

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<sup>268</sup>Fabrizio, C.S. (2011). Physician's perceptions of the Hong Kong Cervical Screening Program: Implications for improving cervical health. (Unpublished doctoral dissertation). University of North Carolina, Chapel Hill, NC.

<sup>269</sup>Levy, B.S. (1998). Creating the future of public health: Values, vision, and leadership. *American Journal of Public Health*, 88(2), 192.

<sup>270</sup> 'Guidances' at <http://www.fda.gov/regulatoryinformation/guidances/default.htm>; accessed 1Apr2012

<sup>271</sup> U.S. Food and Drug Administration. "Fact sheet: FDA Good Guidance Practices, available at <http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm285282.htm>, accessed 1Apr2012.



Release of the FDA Draft Guidance will instigate the pharmaceutical companies to consider the inclusion of pregnant women in drug development planning. Changes to the current process will ultimately be reflected in internal company policies and procedures. This is where change will really happen.

Kingdon's Policy Window theory has been described as 'an evolutionary model of public policy.'<sup>272</sup> In the policy formulation stream, Kingdon says that, "Specialists try out and revise their ideas by...attending conferences, circulating papers, holding hearings, presenting testimony, writing reports, publishing articles, and drafting legislative proposals." The resultant 'primeval soup' of policy proposals then go through "the process of policy evolution, [where] some ideas fall away, others survive and prosper, and some are selected to become serious contenders for adoption."<sup>273</sup>

Kingdon's "window of opportunity," if capitalized on by the entrepreneurs, puts the problem on the political agenda for resolution. This "agenda" can be either a government agenda (key topics on the policy development list) or a decision agenda (developing policies that are moving into position for a definitive decision).<sup>274</sup> This study is dealing with a decision agenda. The FDA draft guidance document has been drafted and is in clearance at the agency. It has not yet been released for public consideration. Once it is released – and that date is unknown – public comment will be solicited for a 60 to 90-day period and then the document will go through a revision process at the agency based on the feedback

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<sup>272</sup> John P. Is there life after policy streams, advocacy coalitions, and punctuations: Using evolutionary theory to explain policy change. *Policy Studies Journal* 2003:32(4):488.

<sup>273</sup> Kingdon, J. (2005). The reality of public policy making. Chapter 6. In Danis, M., Clancy, C., & Churchill, H.R. Ethical Dimensions of Health Policy. New York: Oxford University Press, p. 101.

<sup>274</sup> Lieberman, J.M. (2002). Three streams and four policy entrepreneurs converge: A policy window opens. *Education and Urban Society*, 34(4), 445.

received. The length of time until the release of a revised draft guidance as a 'final guidance' is highly variable. In addition to soliciting written comment, FDA will sometimes hold public hearings on the topic. Interested parties can submit a request to speak at the hearing to present their position, their concerns, or their recommendations.

During the period of public comment, interested stakeholders submit their perspectives, preferences, and proposals for consideration. In the policy stream the formation and refining of policy proposals is a process by which ideas confront, compete, and combine with each other, forming combinations and re-combinations.<sup>275</sup> Stakeholders (identified in Chapter 1), all of whom may respond to the call for public comment, include the general public, pregnant women, their families and their health care providers, women's health advocates, the obstetrical community, maternal/child health organizations, IRBs, the pharmaceutical industry, etc.

Kingdon recommends that the development of proposals be done before the opportunity to submit them arises. One of this study's key informants from PhRMA characterized the industry association as being reactive, not proactive. He was, indeed, unaware that the FDA guidance on this topic was on the 2011 docket – information that is available in the public domain. The White Paper will not only serve to raise awareness of the issue, it will also facilitate industry preparation and response to the call for comments on the FDA draft guidance document.

Should pregnant women be included in the drug development process? The issue has not yet, but is about to become, a significant subject of concern to industry. The inclusion of

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<sup>275</sup>Kingdon, J. (2005). The reality of public policy making. Chapter 6. In Danis, M., Clancy, C., & Churchill, H.R. Ethical Dimensions of Health Policy. New York: Oxford University Press, p. 101.

pregnant women in clinical research has serious practical and financial implications for the pharmaceutical industry. It has the potential to change the way companies perform their core business activity – the development of drug interventions to prevent, ameliorate, or cure diseases. Each pharmaceutical and biotechnology company will need to consider the implications in the context of their own enterprise. Current internal policies and procedures about the drug development process will change; new policies will be implemented. The results of this study are intended to assist the companies and their trade associations, PhRMA and BIO, consider the implications and formulate their responses to the document - to add their voice to the public debate that was going on without their participation.

**a. The Plan for Change in the Policy Stream**

To accomplish this goal, the Plan for Change includes multiple means of getting information in the hands of industry leaders. These communications include a number of questions, considerations, and recommendations to add to the 'primeval soup' of policy proposals.

**Table 7.2 Plan for Change in the Policy Stream: Proposing Solutions\***

<b>Plan #</b>	<b>Goal</b>	<b>Target</b>	<b>Intervention</b>
<b>3</b>	Awareness of <b>potential solutions for industry</b> consideration in guidance responses & internal policies	Industry colleagues, Senior management	White Paper <sup>†</sup> to FDA, PhRMA, BIO, and companies
<b>4</b>	Awareness of <b>potential solutions for companies'</b> draft response	Company colleagues & senior management	Participate in drafting my company's response to FDA
<b>5</b>	<b>Industry perspective included</b> in discussion of the issue	FDA, Stakeholders, Public	Present study findings at FDA hearing, if applicable

\*See Complete Plan for Change in Appendix V.

<sup>†</sup> See White Paper in Appendix VI.

## **Plan for Change Proposals**

3. Propose potential solutions to the issues for consideration in guidance and guidance response.

**Goal:** To assist with the identification and adoption of acceptable solutions to the underrepresentation of pregnant women in clinical research to enable the evidence-based treatment of women with medically compromised pregnancies.

**Target:** the agency, the industry, and the companies

**Intervention:** Provide a copy of the White Paper to the key informants in this study for sharing within their organization and with external colleagues.

4. Provide information and proposed solutions to consider for the company's draft response.

**Goal:** To provide the broader industry perspective to my company to assist with its consideration of the issues and its formulation of a response to the proposed FDA guidance.

**Target:** Company colleagues and senior leaders

**Intervention:** Provide a copy of the White Paper to my colleagues in various departments including Regulatory Affairs, Drug Safety, Medical Affairs, and to the Chief Medical Officer; participate in the working group that authors the FDA response.

5. Add industry perspective to the discussion in the public domain.

**Goal:** Increase awareness of pharmaceutical industry perspectives in the debate about the inclusion of pregnant women in clinical research.

**Target:** The U.S. Food and Drug Administration, the general public

**Intervention:** Present study findings at the FDA hearing, if one is held, and/or share study findings with advocates for use in their presentation to FDA, to inform the agency's deliberations on this draft guidance.

This study resulted in a number of policy, process, and procedural suggestions from the key informants for the three main stakeholders in the debate: FDA, the industry association, and the companies (see White Paper, Appendix VI).

### **b. Public Health in the Policy Stream**

Policy development is one of the three public health core functions identified by the Institute of Medicine in its landmark 1988 report on the future of public health<sup>276</sup> (the others are assessment and assurance). It called upon public health practitioners to promote "the use of the scientific knowledge base in decision-making about public health and by leading in developing public health policy."<sup>277</sup> This study seeks to ensure that there is a scientific knowledge base to inform decision making about the treatment of individual pregnant

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<sup>276</sup>Institute of Medicine Committee on the Future of Public Health. (1998). The Future of Public Health. Washington DC: National Academies Press.

<sup>277</sup> Turnock, B.J. (2009). Core functions and public health practice. In Public Health: What it is and How it Works, 4<sup>th</sup> ed. Sudbury, MA: Jones and Bartlett Publishers, p.222.

women and to encourage the application of the scientific knowledge base to the decision-making process about when and how to study pregnant women overall. The quantitative study adds the benchmark of the proportion of clinical trials that exclude pregnant women to the scientific literature. The qualitative study adds the voice of the pharmaceutical industry, a key stakeholder, to the public discourse.

Guidance documents can be viewed as a type of regulatory policy. Although they do not mandate behavior, their contents are closely adhered to by the industry. Regulatory policies "limit the discretion of individuals and agencies, or otherwise compel certain types of behavior. These policies are generally thought to be best applied when good behavior can be easily defined and bad behavior can be easily regulated and punished through fines or sanctions."<sup>278</sup>

The "policy cycle" is a familiar construct in public health<sup>279</sup> and is applied to this issue in Table 7.3. Knowledge of the cycle assists public health professionals to understand problem solving and where in the cycle to intervene to influence policy.

### **c. Public Health Leadership in the Policy Stream**

"Public health leaders must contribute to national debates; problems that governments face in relation to public health are difficult, and they cannot expect to solve them on their

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<sup>278</sup>Wikipedia contributors. (n.d.). Policy. In *Wikipedia, The Free Encyclopedia*. Retrieved April 1, 2012 from <http://en.wikipedia.org/w/index.php?title=Policy&oldid=484514172>

<sup>279</sup>Association of Faculties of Medicine of Canada. (n.d.). Primer on public health population: The policy cycle. In Howlett, M., & Ramesh, M. (1995). *Studying Public Policy: Policy Cycles and Policy Subsystems*. Toronto: Oxford University Press. Retrieved from [http://phprimer.afmc.ca/Part3PracticeImprovingHealth/Chapter14Decision MakingPoliciesAndEthicsInHealthCareAndPublicHealth/Thepolicycycle](http://phprimer.afmc.ca/Part3PracticeImprovingHealth/Chapter14DecisionMakingPoliciesAndEthicsInHealthCareAndPublicHealth/Thepolicycycle)

own. Public health leaders...contribute to solving these problems. The most successful public health leaders have engaged in the policy process..."<sup>280</sup>

**Table 7.3 Contribution of this study in the policy cycle.**

<b>Stages in Policy Cycle</b>	<b>Phases of problem solving</b>	<b>Description and comments</b>	<b>Contribution of Study</b>
Agenda setting	Problem recognition	FDA creates and releases draft guidance to public.	Notice to stakeholders of impending guidance release, frames problem
Policy formulation	Proposal of solution	Stakeholders formulate and submit perspectives and policy options.	Potential solutions to stakeholders for consideration and submission
Decision-making	Choice of solution	FDA considers all comments to create final guidance.	Participation in solution proposal and adoption process
Policy implementation	Putting solution into effect	Stakeholders consider options, formulate internal policies.	Influence on multiple individual company's internal policy changes
Policy evaluation	Monitoring results	Stakeholders monitor implementation, intended and unintended consequences and continue dialogue with FDA.	Monitoring and evaluation activities for ongoing workstreams

As a public health professional, my intent is to influence the final version of this public policy by contributing the perspective of one major stakeholder to the decision-making process and by participating in the development of public health policy.

<sup>280</sup>McKee, M. (2005). Challenges to health in Easter Europe and the former Soviet Union: A decade of experience. In Foege, W.H., Global Health Leadership and Management, San Francisco, CA: Jossey-Bass, p. 181.

Beyond identifying the issue as a problem, the results of this study will serve to influence my colleagues in industry to consider what industry can do to improve evidence-based care for women experiencing medically complicated pregnancies. In 1983, a rural sociologist, Everett Rogers, published his theory of Diffusion of Innovations<sup>281</sup> – how change is adopted by individuals and organizations. In it, he called 'diffusion' the process by which a new idea or a change in thinking (an innovation) is communicated by members of a social system. The diffusion process includes persons becoming knowledgeable about an issue, persuading others to make a change, making decisions based on the new thinking, implementing the innovation, and then via evaluation, either confirming it as worthwhile or discarding it as ineffective. This process takes place over time. By 1) raising the issue with industry colleagues, 2) persuading them that the issue is a problem, 3) having them articulate potential solutions, 4) providing the proposed solutions to other members of the pharmaceutical industry "social system" at a point in time when it is in their best interest to respond to the FDA's call for comment, the study should lead to decision-making influenced by new thinking. The final FDA guidance document will spur the adoption of the innovation and the industry will certainly evaluate its utility and its cost.

As a participant, rather than a leader, in the industry's social system, I will be using 'influential power' – the capacity of one person to influence another – as opposed to the authority that comes from one's hierarchical position in an organization<sup>282</sup> to stimulate this diffusion of innovation. Yukl defines leadership as a "process of influencing others to understand and agree about what needs to be done and how to do it, and the process of

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<sup>281</sup> Rogers, E.M. (1983). Diffusion of Innovations. New York: Free Press.

<sup>282</sup>Yukl, G. A. (2005). Leadership in Organizations (6<sup>th</sup> edition).New Jersey: Prentice Hall, p. 146.



facilitating individual and collective efforts to accomplish shared objectives.”<sup>283</sup> By providing the White Paper to both individuals within the industry and to the collective leadership at the industry association, the study findings are intended to stimulate individual and collective efforts at innovations to benefit pregnant women and their offspring.

### 3. POLITICAL STREAM

"[T]here is...broad agreement that politics and political issues are rarely analyzed and frequently ignored at all stages of the policy identification, development, and implementation process in the health sector."<sup>284</sup>

FDA put the issue in the political stream when it placed "Pregnant Women in Clinical Trials: Scientific and Ethical Considerations" on the 2011 docket of proposed guidance documents. The government agenda was made clear – regulatory guidance for the pharmaceutical industry is coming. Left to be determined is what the final guidance document will contain.

Kingdon recommended special studies of an identified issue to provide indicators of the existence and magnitude of the issue. He also advocated for the identification and promotion of constituent feedback.<sup>285</sup> This study provides both. Papers and publications are advocacy tools that provide information to public health activists for use in addressing key

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<sup>283</sup>Yukl, G. A. (2005). *Leadership in Organizations* (6<sup>th</sup> edition). New Jersey: Prentice Hall, p. 8.

<sup>284</sup>Glassman, A. & Buse, K. (2008). Politics and public health policy reform. In Heggenhougen, K. & Quah, S. (Eds.), *International Encyclopedia of Public Health, Vol 5*. San Diego: Academic Press. pp. 163-170.

<sup>285</sup>Stachowiak, S. (2009). Pathways for change: Theories about how policy change happens. *Organizational Research Services*. Retrieved from [http://www.organizationalresearch.com/publications\\_and\\_resources\\_featured.aspx](http://www.organizationalresearch.com/publications_and_resources_featured.aspx)

legislators and influencing potential guidance and regulation. Other characteristics that provide political advantage include, "(a) credible information on social conditions, available policy options, and likely impacts; (b) recurrent interactions with policy makers; (c) large and geographically dispersed membership; (d) group cohesion and unified positions on priority issues; and (e) organizational resources."<sup>286</sup> All three major stakeholders: FDA, PhRMA and the Second Wave Consortium, possess these characteristics. This study contributes data for item (a) to the stakeholders so that (d) can be achieved. The intent is to increase recognition of identifiable commonalities, barriers and opportunities, and shared objectives to assist the political process in arriving at acceptable solutions to this issue.

**Table 7.4 Plan for Change in the Political Stream: Long-term advocacy\***

<b>Plan #</b>	<b>Goal</b>	<b>Target</b>	<b>Intervention</b>
<b>6</b>	Increased knowledge of <b>issue in public domain</b>	Advocates, Academia, General public	Additional publications and presentations
<b>7</b>	<b>Personal influence on my company's</b> internal deliberations on issue	Company colleagues & senior management	Continue involvement in issue at my company
<b>8</b>	Issue remains in public and professional consciousness; <b>continued advocacy</b> for increased evidence-based treatment for pregnant women	Second Wave Consortium, PhRMA, other organizations	Continue involvement in issue in other organizations

\*See Complete Plan for Change in Appendix V.

### **Plan for Change Proposals**

**6.** Use the findings of the study to continue to share knowledge of the issue in the public domain.

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<sup>286</sup>Thomas, R.O. (2006). The politics of public health policy. *Annual Review of Public Health*, 27, 195–233.

**Goal:** Keep the issue in the political arena while FDA is considering their policy options. This is a sensitive topic for discourse in the public domain. While advocates for change are seeking improved health outcomes for both the fetus and the pregnant woman (and these two are inextricably linked), women's interests are sometimes characterized as being in opposition to fetal protection. It is easy to react to the question of research on pregnant women with a resounding "no," "of course not," "that would be unethical." Without knowledge of the adverse repercussions, the advantages of such research are counterintuitive. To change that mind-set, the adverse consequences of the lack of research for pregnant women must be broadly, but carefully, communicated.

**Target:** Advocates, academia, the general public

**Intervention:** Utilize the findings of the study to create additional publications and presentations. The Addendum to the dissertation, which contains my analysis of key informant responses to the interview questions, provides additional rich data with which to address different perspectives of the issue. For example, the ethics, the costs, and the risks to pregnant women of conducting versus not conducting research studies, could all be further explored. Implications for the Institutional Review Boards, the principal investigators, and the research institutions at which they conduct studies could be addressed. The willingness of pregnant women whose pregnancies are threatened by illness to participate in research studies should be explored. Discussing these issues in the public domain would make the subtleties of the issue more explicit and refine the possibilities for addressing them.

7. Use findings of the study to influence from within.

**Goal:** Politics are not confined to the government. Politics exist in all organizations.

Each pharmaceutical company will consider the potential impact of the FDA guidance within their own organization. Dissemination of the study findings to each of the key informants that work within the pharmaceutical and biotech industry has the potential to impact the decision-making within that institution.

**Targets:** Pharmaceutical company colleagues, senior management within industry

**Interventions:**

a) Dissemination of study findings via the White Paper to the key informants in this study with instructions to share freely with their colleagues within and outside of their companies.

b) Present the findings of this study in the context of a new maternal health initiative at the pharmaceutical company where I work. The goal of the program is to apply "scientific and business expertise to making proven solutions more widely available, developing new game-changing technologies, and improving public awareness, policy efforts, and private sector engagement" for improving maternal health worldwide. I will engage the director of the program and other senior leaders in a discussion about how the company could improve its support for pregnant women *within* the company. Sharing the results of this study and the recommendations of industry key informants, I will suggest that the company, in keeping with its new initiative, could be a forerunner and model for the industry in the expansion of the inclusion of pregnant women in clinical trials.

**8.** Use findings of the study to continue to advocate on behalf of pregnant women.

**Goal:** To disseminate the findings of the study for use by multiple organizations who advocate on behalf of pregnant women

**Targets:** Professional organizations, PhRMA, and the Second Wave Coalition

**Interventions:**

a) I have been or am currently involved in several organizations whose mission is the improvement of maternal child health (Organization of Teratology Information Specialists, the Teratology Society, ISPE [International Society of Pharmacoepidemiologists] Medications in Pregnancy special interest group, the Global Health Council, and APHA [American Public Health Association] Reproductive Health special interest group)). I will continue to work with and within these organizations, and will offer to contribute the findings of this study to these groups in the belief that broadening the inclusion of pregnant women in clinical studies will improve maternal health.

b) I have only recently become involved in the Second Wave Consortium but will continue to work with them as a contributor in the advancement of their mission. I will, of course, offer them my study data for further use, communication, and dissemination. I will suggest that they convene a meeting with Consortium members and industry leaders to discuss the impending FDA Guidance release.

c) In further communication with the industry association (in addition to providing the White Paper) I will suggest to PhRMA that they create (or recreate, as I believe they used to have) a working group on Issues in Maternal Health.

## **b. Public Health in the Political Stream**

Some participants in the policy stream come to the convergence more prepared than others. FDA and the Second Wave Consortium have been working on this issue, often behind closed doors, for many years. The pharmaceutical industry, in my mind, comes to this issue in the weakest position of the three major players. Unlike its power position in determining whether to include pregnant women in individual clinical trials, it appears to be unprepared for the debate about the inclusion of pregnant women in clinical research in general.

Nonetheless, industry is a powerful political constituent with well organized lobbyists and a network of connections. It is also the subject matter expert on how to develop drug therapies and design clinical trials to test their effectiveness and safety. While the industry may be in a weakened position because it has not been paying attention to the issue, it will be motivated to respond when the time comes. As Thomas Oliver points out, "Any proposed change to policy threatens the existing distribution of benefits and costs, and groups with an identifiable stake in the outcome," like the pharmaceutical industry, "will organize themselves in the political system" in response. He continues, "The targets of regulatory policies can make policy implementation extremely difficult. Organizations... facing concentrated costs will likely continue to resist or seek opportunities to renegotiate the original policy."<sup>287</sup> Therefore, it is important to get information into their hands. Improved awareness of the issue, a better understanding of the pervasiveness of the practice, and

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<sup>287</sup>Oliver, T.R. (2006). The politics of public health policy. *Annual Review of Public Health*, 27, 209-223.

potential solutions to the problem – suggested by knowledgeable researchers from within the companies – provides the basis upon which to participate in the political process.

### **c. Public Health Leadership in the Political Stream**

"Public health professional who understand the political dimensions of health policy can conduct more realistic research and evaluation, better anticipate opportunities as well as constraints on governmental action, and design more effective policies and programs."<sup>288</sup> The topic of this study has obvious – and difficult – political implications. From the involvement of a powerful and highly regulated industry to the publicly debated (and privately held) opinions regarding fetal protection and women's reproductive health, the subject of this study is controversial and politically charged. This study provides quantitative and qualitative data to ground the debate in information and policy proposals from a key, and previously absent, stakeholder so that all voices can be represented at the table.

"Public policy is not a single act of government but a course of action that involves individuals and institutions in both the public and private sectors, and encompasses both voluntary activities and legal injunctions."<sup>289</sup> Currently, pharmaceutical companies can make voluntary and individual decisions as to the inclusion of pregnant women in the clinical trial process. While an FDA Guidance does not mandate action, the industry usually adopts its recommendations. And sometimes, when the industry has been slow to adopt initiatives

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<sup>288</sup>Oliver, T.R. (2006). The politics of public health policy. *Annual Review of Public Health*, 27, 209- 223, p. 195.

<sup>289</sup>Oliver, T.R. (2006). The politics of public health policy. *Annual Review of Public Health*, 27, 209- 223, p. 219.

voluntarily, regulations will follow – as was seen with the pediatric drug testing initiatives. With the release of the new guidance on the inclusion of pregnant women in clinical trials, the industry will have to weigh the pros and cons of adopting new innovations in the assessment of drug safety and efficacy in pregnant women. And other stakeholders will monitor whether those efforts are enough to improve the evidence-base for treatment decisions – or if legislative action will be needed.

One of the key informants in this study, who has significant political insight and experience, encouraged me to pursue this issue via the legislative process:

*"Politically," he said, "I think it needs to be on the agenda of Pharma and Bio. It's got to get on their agenda so that the industry or the sector as a whole can be supportive to varying degrees. This is the kind of thing that can show up in the next PDUFA (Prescription Drug User Fee Act)[renewal]. It could be on the legislative agenda for 2017. Remember, that starts in 2015 - there's a fair lead time. So you really need to be developing those discussions now in order to have any chance of getting on [the PDUFA] agenda for 2017.*

PDUFA, first passed in 2002 and renewed every 5 years since, allows FDA to collect user fees from the companies who are applying for a new drug approval to help pay for the resources required to perform the application's review. In response to complaints of prolonged reviews restricting access to new treatments, especially for HIV, the Act significantly improved the number of reviewers at FDA and decreased the amount of time it takes for a drug – or device or biologic – to get through the approval process. FDA, PhRMA, and the general public all in favored of the regulation. In 2007, the PDUFA renewal was part of the Food and Drug Administration Amendments Act which included initiatives like requiring pediatric drug testing, rewarding developers of treatments for neglected diseases,



and mandating the posting of clinical research studies on ClinicalTrials.gov. The key informant is suggesting that continuing advocacy, research, and leadership on this issue could lead to regulation that will provide incentives, encouragement, or requirements to include pregnant women in clinical research in the 2017 PDUFA renewal.

Pharmaceutical companies participate in this process through PhRMA. Conducting this study, talking to members of PhRMA, and providing them with a white paper on the topic establishes my credibility as a subject matter expert in the field. If my persuasion results in the establishment of a working group on Issues in Maternal Health, I may continue to be involved in the legislative process.

Whether legislation will be needed or whether the voluntary approach will provide enough positive change to be acceptable to the stakeholders will be decided by the impact of the guidance formation, implementation, and evaluation process. Adoption of innovation by the pharmaceutical industry may be the determining factor as to whether legislative reform will be required. Additional research, monitoring, and evaluation will be needed. And ongoing leadership via advocacy, communication, persuasion, bargaining, positional power, and political pressure will be required.

### **C. Evaluation**

#### **1. Evaluation of the Impact of the Plan for Change**

When the FDA Guidance is final, the pharmaceutical industry will implement its recommendations. While guidance documents are non-binding, their recommendations are

difficult to ignore and companies usually conform. Table 7.5 presents the measures of success for the Plan for Change.

**Table 7.5 Evaluation of the Plan for Change**

<b>Problem</b>	<b>Intervention</b>	<b>Evaluation method</b>	<b>Measure of success</b>
<b>Lack of awareness of issue as problem</b>	White Paper frames issue	Monitor literature and industry publications and workshops on topic	An increase in publications, articles, conference sessions on this topic
<b>Lack of awareness of current practice</b>	Publication on current practice		
<b>Lack of potential solutions</b>	White Paper contains solutions		Publications, sessions discuss solutions
<b>Industry need to respond to draft guidance</b>	Work with Company and PhRMA on draft responses	Review content of submitted PhRMA and company responses	Content of response documents reflect awareness of issue and recommendations for change from current practice
<b>FDA need to determine final guidelines</b>	Participation in FDA hearing (if applicable)	Monitor content of stakeholder presentations	Final guidance includes recommendations to include pregnant women in clinical research
<b>Implementation of guidance within companies</b>	White Paper contains recommendations	Changes in companies' policies and procedures	Changes in company policies that increase the potential for the participation of pregnant women in studies
<b>Evaluation of impact on inclusion of pregnant women in clinical research</b>	Ongoing involvement as SME	Repeat quantitative study; monitor literature; participate in interest groups	Actual increase in proportion of clinical trials that do not exclude pregnant women or that are designed for pregnant women
<b>Evaluation of impact on treatment of pregnant women</b>	Ongoing involvement as SME	Repeat qualitative study, including HCPs; review drug labels for use in pregnancy	Key informants indicate an improvement in evidence-based practices; Increased proportion of drug labels include evidence-based guidelines for use in pregnancy

## 2. Evaluation of the Impact of the FDA guidance

There are a number of evaluations that were published following the implementation of the pediatric rule requiring clinical trials for the pediatric population. These include, for example, Improving Pediatric Dosing through Pediatric Initiatives: What We Have Learned;<sup>290</sup> Assessing the Effects of Federal Pediatric Drug Safety Policies;<sup>291</sup> and Economic Return of Clinical Trials Performed under the Pediatric Exclusivity Program,<sup>292</sup> etc. The methodology these authors used is easily transferable to the evaluation of advances in the study of pregnant women. Such measures include evaluating changes to drug labeling that include information specific to use during pregnancy including: pregnancy indications, dosing changes in pregnancy, pharmacokinetic information, new safety information, and information concerning efficacy or lack thereof. Cost savings can be calculated from change to current costs for maternal and neonatal hospitalizations, morbidity from adverse drug reactions, and maternal illness-induced decreased productivity. However, these calculations would have to wait until drug testing in pregnant women was widely implemented.

These cost calculations could actually get at the public health impact of the guidance, which would be extremely important to know. I anticipate that the return on investment of this initiative may be difficult to measure in cost savings alone because the market for individual drugs used in medically compromised pregnancies is low and the recipients are

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<sup>290</sup>Rodriguez, W., Selen, A., Avant, D., Chaurasia, C., Crescenzi, T., Gieser, G.,...Uppoor, R.S. (2008). Improving pediatric dosing through pediatric initiatives: What we have learned. *Pediatrics*, 121(3), 530-539.

<sup>291</sup>Dor, A., Burke, T., & Whittington, R. (June, 2007). Assessing the effects of federal pediatric drug safety policies. *The George Washington University Medical Center Newsletter*, pp. 1-16.

<sup>292</sup>Li, J., Eisenstein, E.L., Grabowski, H.G., Reid, E.D., Mangum, B., Schulman, K.A. ...& Benjamin, D.K. (2007). Economic return of clinical trials performed under the Pediatric Exclusivity Program. *Journal of the American Medical Association*, 297(5), 480-487.

geographically dispersed. I would refer back to the experts in advocacy and communication who recommended the use of framing issues in social justice terms and the use of anecdotes to convey meaning. Could we ask clinicians in the obstetric field to collect stories on how the information has impacted their practice of medicine and the lives of the pregnant women and their babies who participated in clinical trials or benefitted from the use of a dose-adjusted therapy in pregnancy? That's where the real impact would be found and its collection and communication will rely upon professional organizations and patient advocacy groups.

Evaluation of potential negative impact and unintended consequences should also be undertaken. Estimating the cost of conducting the trials in pregnant women, increased litigation due to adverse outcomes, and birth defects or other morbidity attributed to drug exposures in clinical trials would be at the top of the list. The industry would certainly monitor the impact of the guidance on the pharmaceutical company – the costs of conducting the trials and the related infrastructure and administration of them - against any financial returns (which would be expected to be small).

How does one measure the return on investment (ROI) for corporate responsibility (CR) measures? Customer and employee satisfaction scores are suggested as potential "soft-indicators" of impact on corporate responsibility scores. These scores are not to be underestimated – pharmaceutical companies compete to get higher ratings on CR indicator scales such as the Corporate Social Responsibility Index, the Access to Medicines Index, and the Human Rights Impact Assessment score. An effort to get a question about the inclusion of pregnant women in clinical studies on a pharmaceutical industry-focused measurement scale would focus attention on the issue. How one achieves that goal would be worthwhile exploring.

New policy implementation and evaluation necessitates the need to monitor and measure both intended and unintended outcomes. Based on the outcomes of these measurements, policy modifications can be made for improvement in both the process and the intended outcomes.

#### **D. Conclusion**

John Kingdon's "Policy Window" theory of change provided the conceptual framework for the planning, implementation, and application of findings of the study. The participation of pregnant women in clinical research has advocacy, policy, and political implications, therefore the plan for change can be framed within Kingdon's constructs. In order to elicit change in social issues, he recommended obtaining constituent feedback and indicators of the existence and magnitude of the issue via research. The results of this research study provide this factual information that was missing from the literature and from prior discourse. Problem recognition, policy solutions, and political participation are enabled and the pharmaceutical industry can join into the debate. While identifying opportunities and ideas for implementing change, the study also identified perceived barriers that must be overcome – in clinical research design, in perceptions of ethical conduct, in economic impact, in public support, and in litigation risk. Much effort will need to be sustained over many years to make the inclusion of pregnant women in clinical research a reality. (See Chapter 8 for suggestions for future research.)

## Chapter 8

### Discussion

#### A. Impact on public health

In the U.S., more than a third of the 1.7 million women who give birth each year experience some type of adverse complication<sup>293</sup> - and two women die every day from pregnancy-related causes.<sup>294</sup> Over 60 percent of pregnant women are prescribed one or more medications (not including vitamins)<sup>295,296</sup> but the safety of their use during pregnancy is largely unknown.<sup>297</sup>

Also unknown, and equally important, are the negative consequences of not taking a medication, taking less of a medication, taking a different medication, or discontinuing a medication. I am personally aware of adverse consequences such as the recommendation of ineffective treatment to pregnant women exposed to anthrax, the termination of wanted

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<sup>293</sup> Daniel, I., Berg, C., Johnson, C.H., & Atrash, H. (2003). Magnitude of maternal morbidity during labor and delivery: United States, 1993-1997. *American Journal of Public Health*, 93(4), 631-634.

<sup>294</sup> Heron, M., Hoyert, D.L., Murphy, S.L., Xu, J., Kochanek, K.D., & Tejada-Vera, B. (2009). Deaths: Final data for 2006, National Vital Statistics Reports, 57(14), I-136, p. 116. Retrieved from [http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57\\_14.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf)

<sup>295</sup> Andrade, S.E., Gurwitz, J.H. & Davis, R.L. (2004) Prescription drug use in pregnancy. *American Journal of Obstetrics and Gynecology*, 191, 398-407.

<sup>296</sup> Glover, D.D., Amonkar, M., Rybeck, B.F. & Tracy, T.S. (2003). Prescription, over-the-counter, and herbal medicine use in a rural obstetric population. *American Journal of Obstetrics & Gynecology*, 188(4), 1039-1045.

<sup>297</sup> Lo, W.Y. & Friedman, J.M. (2002). Teratogenicity of recently introduced medication in human pregnancy. *Obstetrics & Gynecology*, 100, 465-473.

pregnancies due to unfounded fears of birth defects from exposure to a vaccine, and the death of a pregnant woman who ceased taking her asthma medication due to an unwarranted fear that the medication would cause harm to her fetus.

In any pregnancy, there is an overall approximate 3 per cent risk of delivering a baby with a birth defect.<sup>298</sup> Most of the causes of these congenital anomalies are unknown and medication exposures are known to induce a very small percent of these defects.<sup>299</sup> In fact, the vast majority of drugs and vaccines do not cause fetal harm.<sup>300</sup>

Pregnant women get sick. In addition to pregnancy-specific complications like gestational diabetes and pre-term labor, medical conditions that occur in non-pregnant women occur in pregnant ones as well, including psychiatric illness, cancer, and infectious diseases. These conditions can have a devastating impact on the health of the pregnant woman and on the well-being of her fetus. Women's health care practitioners lament that the "current evidence base for the care of pregnant women facing illness is widely regarded as deplorable."<sup>301</sup>

To discover the most effective therapeutic interventions to treat illness, the scientific community conducts systematic research. But pregnant women are largely excluded from

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<sup>298</sup>Centers for Disease Control and Prevention. (2011). Birth defects. Washington, DC: Author. Retrieved Oct. 28, 2011 from <http://www.cdc.gov/ncbddd/birthdefects/data.html>

<sup>299</sup>Brent, R.L. (2004). Environmental causes of human congenital malformations: The pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics*, 113(4), 957-968, p. 958.

<sup>300</sup>Koren, G., Pastuszak, A., & Ito, S. (1998). Drugs in pregnancy. *New England Journal of Medicine*. 338, 1128-1137, p. 1131.

<sup>301</sup>Lyerly, A.D., Little, M.O., & Faden, R.R. (2011). Reframing the Framework: Toward fair inclusion of pregnant women as participants in research. *The American Journal of Bioethics*, 11(5), 50-52, p. 51.

such research despite the recommendations of subject matter experts like the U.S. Food and Drug Administration<sup>302</sup>, the Institute of Medicine,<sup>303</sup> the Council for International Organizations of Medical Sciences,<sup>304</sup> and The American College of Obstetricians and Gynecologists.<sup>305</sup> This study's findings confirmed that the pharmaceutical industry excludes pregnant women based primarily on the beneficent desire to avoid harming a fetus and the economic intent to avoid the financial and reputational risk of potential litigation. But the absence of research data on the safety and efficacy of medications compels clinicians and their pregnant patients to make treatment decisions based on past practices, educated guesses, and gut feelings. We must do better.

Key informants in the study identified barriers to and opportunities for broadening the inclusion of pregnant women in clinical research so that FDA, the pharmaceutical companies, and other stakeholders can knowledgeably debate the issue and identify acceptable and effective ways to conduct research with and for pregnant women. The primary recipient of the outcome of this debate is the FDA draft guidance document, "Pregnant Women in Clinical Trials: Scientific and Ethical Considerations" which is scheduled for release in 2012. Public comment will follow its release and the pharmaceutical industry will respond with its reactions to the proposals in the draft.

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<sup>302</sup>Feibus, K. & Goldkind, S.F. (May 17, 2011) Pregnant women and clinical trials: Scientific, regulatory, and ethical considerations. Oral presentation at the Pregnancy and Prescription Medication Use Symposium, Silver Springs, MD.

<sup>303</sup>Mastroianni, A.C., Faden, R., & Federman, D. (Eds). (1994). Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine. Washington, DC: National Academy Press.

<sup>304</sup>Council for International Organizations of Medical Sciences. (2002). International ethical guidelines for biomedical research involving human subjects. Retrieved April 17, 2011 from [www.cioms.ch](http://www.cioms.ch).

<sup>305</sup>American College of Obstetricians and Gynecologists' Committee on Ethics. (2007). ACOG committee opinion: Research involving women. *Obstetrics & Gynecology*, 110(3), 731-736, p. 732.



This study identified research methods that can be used so that pregnant women with medically compromised pregnancies can receive treatment within research protocols that minimize the risks to the mother and the fetus. The benefits of the research studies must exceed the risks and the pregnant woman must be receiving therapeutic benefit or the protocols would be unethical. Key informants from within the pharmaceutical industry identified recommendations for research practices that meet these requirements. This information will be shared with multiple recipients within the industry and associated stakeholders like IRB members and the FDA. By providing the data to the industry association, industry colleagues, and key opinion leaders within my own pharmaceutical company, the study results will influence the content of the industry's response to the draft guidance. By providing the data to FDA by sharing the results with the agency key informant and potentially testifying at the FDA hearing, the study findings will influence deliberations on the draft guidance content. Ultimately, both activities will affect the final version of the FDA guidance document.

Practices recommended in agency guidance documents are widely adopted by the pharmaceutical industry. Therefore, this study's influence on the content of the guidance will impact research practices in the pharmaceutical industry. The broader inclusion of pregnant women in clinical research studies will improve clinical knowledge to decrease inadequate treatment, reduce maternal morbidity and mortality, and diminish the unnecessary termination of wanted pregnancies – all consequences of a lack of information about the safety and efficacy of medications used to treat illness during pregnancy.

## B. Limitations of the Study

In addition to the limitations of the study methodology articulated in the Methods and Results (Chapters 4, 5 and 6), the study assumes that, if invited, pregnant women will participate in clinical studies. However, pregnant women's willingness to participate in clinical studies is largely unknown. One small study found that 95% of pregnant women interviewed said that they would participate "if there is a chance that participation in a clinical trial would help their pregnancy and improve their baby's health."<sup>306</sup> Further research should be done to articulate the voice of this key constituent as patient advocacy will be necessary to achieve change. Patient advocates were an important constituency in changing clinical trial policies to include women of childbearing potential in clinical studies, to include infected women in HIV studies, and to conduct studies on breast cancer treatment.

This study also assumes that the industry will listen to the many arguments in favor of including pregnant women in clinical studies. I think that the primary aversion to inclusion – the desire to do no harm to the fetus – can be overcome by innovations in preclinical testing, research design, and timing of the studies as discussed earlier in this document. However, the economic justifications for the exclusion of pregnant women in clinical research – an actual increase in research costs and a perceived risk of litigation – will be harder to overcome. The current economic climate is not friendly to potentially costly new initiatives based on considerations of social justice, shared responsibility, cooperation, or obligation to the collective good. Such proposals are 'nice-to-haves' that don't make the cut during a financial

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<sup>306</sup>Rodger, M.A., Makropoulos, D., Walker, M., Keely, E., Karovitch, A., & Wells, P.S. (2003). Participation of pregnant women in clinical trials: Will they participate and why? *American Journal of Perinatology*, 20(2), 69-76.

downturn. The pharmaceutical industry is currently executing downsizings, mergers, outsourcing, and decreases in research and development in an effort to cut costs and maintain profit in a recessionary environment. So, while key informants within the companies may understand the need to include pregnant women in research and support their inclusion, they are not the business leaders who must make the difficult decisions that cut potentially promising programs or decline to support corporate responsibility proposals.

The alternative to broadening the inclusion of pregnant women in clinical studies is to continue the current practice of their exclusion. FDA guidelines can be ignored. The OPRU sites will conduct PK testing on priority medications for important diseases; pregnancy registries will continue to collect exposure outcomes over time; population-based registries in European countries will provide data, and electronic health and insurance records will enable case-control studies – all of which, however, take years to arrive at informative data. In the meantime, pregnant women will continue to be misinformed, undertreated, overdosed, and mistreated. I fear that, unless public pressure is applied, significant incentives are offered, and/or protection from litigation is devised, the status quo may remain the norm. So, in addition to my efforts to bring this study's findings into the hands of individual companies, the industry association, and the public domain, advocacy efforts and economic pressures from other influential stakeholders will be needed. A new workshop by advocates of broader inclusion – health care providers, ethicists, pregnant women, academics, FDA, and this time with the pharmaceutical industry invited to participate – should be held to negotiate potential solutions, incentives, protections, and results. Change can occur if the problem stream convincingly articulates the issue as a problem, the policy stream contributes acceptable solutions, and the political stream provides sufficient pressure to induce change. Such a

trifecta might then ensure that, when the policy window closes, the new policy behind the window will be favorable to pregnant women.

### **C. Ethical Considerations**

In this study's area of inquiry, where both the pros and cons of the inclusion of pregnant women in research can be argued on ethical merits, an ethical framework can assist to provide structure to the debate. In Chapter 3, I reviewed the ethical principles and theories most frequently invoked when discussing clinical research, medical practice, women's interests, and business practices and concluded that guidance for evaluating perspectives about the inclusion of pregnant women in clinical research should be based upon the ethical principles of Autonomy, Beneficence, Justice, the Ethic of Care, and Stakeholder Considerations (including as stakeholders both the pregnant woman and her caregivers and the drug company and its researchers).

These principles are actualized in the Ethical Guidance below. I propose that stakeholders in the discussions that will occur following the release of the draft guidance use this approach to evaluate the proposals to include pregnant women in clinical research. It may be particularly useful in workshops or conference settings where stakeholders meet to discuss potential solutions. Following Beauchamp's recommendation to frame issues using public health core values,<sup>307</sup> the guidance is intended to assist with the understanding and consideration of ideas, opinions, and options. Translating the essence of the ethical principle

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<sup>307</sup>Dorfman, L., Wallack, L., & Woodruff, K. (2005). More than a message: Framing public health advocacy to change corporate practices. *Health Education and Behavior*, 32(3), 320-336.

into a question format facilitates the application of the principles to the situation. It helps to change the ethical debate from a lofty, unreachable ideal, to a concrete application of the ethical intent. It can facilitate the recognition and consideration of the impact of the proposal from multiple stakeholders' perspectives.

For example, if there is a proposal to wait until the results of Phase III clinical trials are complete before studying a new drug in pregnant women, how does that proposal stand up to the questions in the table? If the proposal is to allow women who become pregnant during a clinical trial the option to remain in the study, how does that proposal stand up to the questions in the table?

**Table 8.1 Ethical Guidance: Application of ethical principles to proposed solutions**

**Autonomy/Respect:**

Does this rationale/solution impinge on anyone's personal autonomy?  
Do all relevant parties consent to this rationale/solution? If not, what are the objections?  
Are all opinions acknowledged and respected?

**Beneficence:**

Who benefits from this rationale/solution and in what way?  
Does the rationale/solution use the best of our current knowledge?  
Does the rationale/solution favor the balance of benefit over risk?

**Non-maleficence:**

Who may be harmed by this rationale or the implementation of this solution?  
How have the potential harms been minimized?  
Are risks communicated in a truthful, complete, and open manner?

**Justice:**

Is the rationale/proposed solution equitable to all stakeholders?  
Can it be made to be more equitable?  
Are the benefits and the burdens fairly distributed among stakeholders?

**Ethic of Care:**

Whose needs are being met by this solution?  
Does the rationale/solution promote cooperation among stakeholders?  
Are relationships identified and maintained or promoted by the action?

**Stakeholders:**

Have all parties involved in this rationale/solution been identified?  
What parties are impacted by this rationale/solution and in what way?  
Are all stakeholders' concerns respected and addressed?  
Do they agree on the solution?

Adapted from Beauchamp & Childress, *Principles of Biomedical Ethics*<sup>308</sup>

**D. Conclusion**

The results of this study support a change in the current practices of the U.S. pharmaceutical industry to broaden the inclusion of pregnant women in clinical studies when appropriate. The findings indicate that there is support within the industry to modify regulatory guidance and clinical research inclusion and exclusion criteria. Alternative research designs and other legal, regulatory, and public policy solutions that address sustaining beneficence and reducing litigation risk are proposed. Improved maternal-infant health outcomes due to the enhanced knowledge of medication efficacy and safety gained from clinical studies in human pregnancies is this study's contribution to public health.

Much as the release of the FDA draft guidance will provoke industry to respond to the issue, the findings of the study will challenge industry to confront fundamental viewpoints, and spur scientists and researchers to find new ways to contribute to clinical knowledge about the safe and effective treatment of pregnant women who need medical intervention. The business reservations about implementing the necessary changes will need to be addressed. But the wealth of knowledge, passion, and willingness to change that this study found within companies to confront this challenge portends an improvement in the contribution that industry will make to maternal health.

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<sup>308</sup>Beauchamp, T. & Childress, J. (2001). *Principles of Biomedical Ethics* (5<sup>th</sup> ed.) Oxford: Oxford University Press. In The Office of Public Policy and Ethics (2002), *A primer to ethical analysis*. Retrieved March 6, 2011 from The University of Queensland web site: <http://www.uq.edu.au/oppe>

## **E. Suggestions for Further Research**

This study identified several opportunities for further research that would contribute knowledge to the field and provide further incentives to change.

### Cost Benefit Analyses

When addressing senior executives in a business environment, in addition to using language and anecdotes that speak to individual and collective values, we can and should also speak in the language of 'market justice.' This study identified missing information that could be helpful in making the case for change to company officials.

- A cost-benefit analysis on the lack of efficacy of amoxicillin against anthrax
  - What are the financial and social implications of that finding?
- A cost-benefit analysis of the exclusion of pregnant women from clinical trials
  - Comparative morbidity and mortality
  - Implications of cost to the health care system
  - Implications of cost to the pharmaceutical industry
  - Social and financial costs (e.g., thalidomide or Bendectin as case studies)

### Research priorities for pregnant women

There is a need to identify what diseases and drug classes would be a priority for pregnant women. What are current treatment practices for these conditions and how could they be improved? Are "older" interventions being used that could be replaced with "newer"

treatments? Case studies that illustrate the implications of this lack of knowledge should be accumulated. The evaluation of the impact of the inclusion of pregnant women could then be measured against such case studies.

### Ex-US Studies for Global Harmonization

This study limited its focus to the inclusion of pregnant women in clinical trials in the United States. But clinical trials are rarely performed in only one country anymore and medical product markets are global. It would be informative to review how the other two major markets' (EU and Japan) regulations, guidelines, and practices regarding pregnant women in research differ from the U.S. Understanding how policy is changed in those political constituencies would be helpful to the potential harmonization of research practices throughout the world.

A key informant suggested that:

*"The other place you can have potential impact is in Europe with EMA (the European Medicines Agency). EMA may have similar interests and it may be possible to explore that. ICH (the International Council on Harmonization) is semi-moribund at the moment but it's entirely possible that they could open up a whole new section to deal with this issue, at least to get the ideas on the table."*

### Potential FDA Incentives

Identify potential incentives that FDA could use to encourage pharmaceutical companies to design and implement studies that include pregnant women. What incentives



have been used in the past, under what circumstances, and have they been successful? What new incentives might be tried? Do incentives replace the need for regulations?

### Litigation and Compensation Protection

From the UTMB conference report:<sup>309</sup>

"There should be a nationally supported mechanism to protect private sponsors and industry from excessive or inordinate liability claims and to develop incentives to promote industry-supported research on this population."

From Moral Science: Protecting Participants in Human Subjects Research:<sup>310</sup>

#### Recommendation 3: Treating and Compensating for Research-Related Injury

"Because subjects harmed in the course of human research should not individually bear the costs of care required to treat harms resulting directly from that research, the federal government, through the Office of Science and Technology or the Department of Health and Human Services, should move expeditiously to study the issue of research-related injuries to determine if there is a need for a national system of compensation or treatment for research-related injuries."

What is the current status of the Presidential Commission's recommendation to explore a national system of compensation for research-related injury? Is the Commission including industry-sponsored research in its scope? Is the Commission aware that the adverse health consequences caused by the exclusion of pregnant women from clinical research are

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<sup>309</sup> Goodrum LA, Hankins GDV, Jermain D, Chanaud CM. Conference report: Complex clinical, legal, and ethical issues of pregnant and postpartum women as subjects in clinical trials. *Journal of Women's Health* 2003; 12(9):864.

<sup>310</sup> Presidential Commission for the Study of Bioethical Issues. (2012). Moral Science: Protecting Participants in Human Subjects Research. Washington, D.C., 2011. Retrieved from <http://bioethics.gov/cms/node/558>

abetted by the pharmaceutical industry's defensible fear of the cost of compensation for causal or unproven but associated fetal injury? Might this topic be of interest to the Commission?

What is the history of the Vaccine Injury Compensation Program? How did that program come to be established? Has it been successful? What are the benefits, detriments, and costs? Could a similar program be established to remove the barrier of litigation risk from the decision to include pregnant women in clinical research?

### Ethics

"...extend the scope of responsibility for ethical research to industry leaders, elected officials, and research funders, because they too play a role in ensuring that research endeavors do not create or perpetuate vulnerabilities, particularly inequalities in health or relations of power."<sup>311</sup>

More fully explore the ethical arguments for and against the inclusion of pregnant women in clinical research. Explore the application of feminist ethics to the issue. How do codes of research ethics change over time? How are they formally and informally adopted by constituencies?

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<sup>311</sup>Eckenwiler, L.A., Ells, C., Feinholz, D., & Schoenfeld, T. (2008). Hopes for Helsinki: Reconsidering vulnerability. *Journal of Medical Ethics*, 34(10), 765-766, p. 766.

### Vulnerable populations:

- Take each of the vulnerable populations as defined in the Common Rule. What impact has the label had on the group? What is the current research practice for each group? Has it had a positive or negative impact? Has it impacted all groups in the same way?
- Explore the history of the inclusion of children in clinical research and the development of the current regulations (Best Pharmaceuticals for Children Act, Pediatric Research Equity Act). What lessons can be learned from that history that could be applied to the current controversy over pregnant women in clinical research? Are these regulations considered to have been successful? What changes would be recommended today?

### Pregnant women's participation in research

Because pregnant women have been routinely excluded from clinical studies we do not know to what extent they might volunteer to participate. Of course, pregnant women would only be asked to participate if they are in need of treatment and the study would potentially provide therapeutic benefit and if the potential benefits of the study exceeded the potential risks. Under those circumstances, participation would be very much like treatment in clinical practice with the added benefit of improved informed consent, enhanced pregnancy monitoring, and the patient's knowledge that she has contributed her experience to the accumulated medical knowledge base to assist other pregnant women. Research has shown that people participate in clinical research studies for many reasons including access to otherwise unavailable treatments. Other motivations include: "closer monitoring than in

routine practice, getting attention for other ailments, better physical and laboratory health checks, superior physicians, labs, and testing, more contact with the providers,....remuneration, and contributions to society."<sup>312</sup>

A survey of pregnant women who are participating in clinical studies should be conducted to ascertain their motivations – why did they agree to enroll? How much influence did making a contribution to medical knowledge contribute to their decision? What were their other considerations? This study determined that there were 5 studies currently ongoing that were specifically designed for pregnant women and 19 studies that would consider enrolling pregnant women. This would constitute a small sample but one that would provide much needed information if we hope to encourage the enrollment of pregnant women – or overcome the mindset that says that pregnant women would never agree to participate.

Finally, the study could be repeated if the enrollment of pregnant women in clinical research becomes more widespread. One could then see how attitudes, beliefs, and practices have changed over time and if the proportion of clinical trials including or designed for pregnant women has improved.

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<sup>312</sup>Iber, F.L., Riley, W.A., & Murray, P.J. (1987). *Conducting Clinical Trials*, New York: Plenum Press. In Merton, V. (1993). The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. *American Journal of Law & Medicine*, 19(4), 369-451, p. 378.

## APPENDIX I

### The Ethical Principles Invoked For and Against the Inclusion of Pregnant Women in Clinical Research.

#### Ethical rationale for the *exclusion* of pregnant women from clinical research

Principle	Rationale
Beneficence	Act in the best interest of the patient: use treatments and study designs that present the least risk.
Non-maleficence	Protect mother and fetus from harm by avoiding experimental drug toxicity with no assurance of safety and avoid exposure without benefit: uninterpretable data.
Financial stewardship	Cost outweighs benefit: litigation risk; little return on investment; and inclusion, which complicates the study, is not required.
Avoid the Double Effect	Beneficence and non-maleficence may conflict when, in trying to do good, harm may be done.
Good clinical practices standards <sup>a</sup>	Use standard, acceptable practices based on current knowledge to achieve good outcomes.

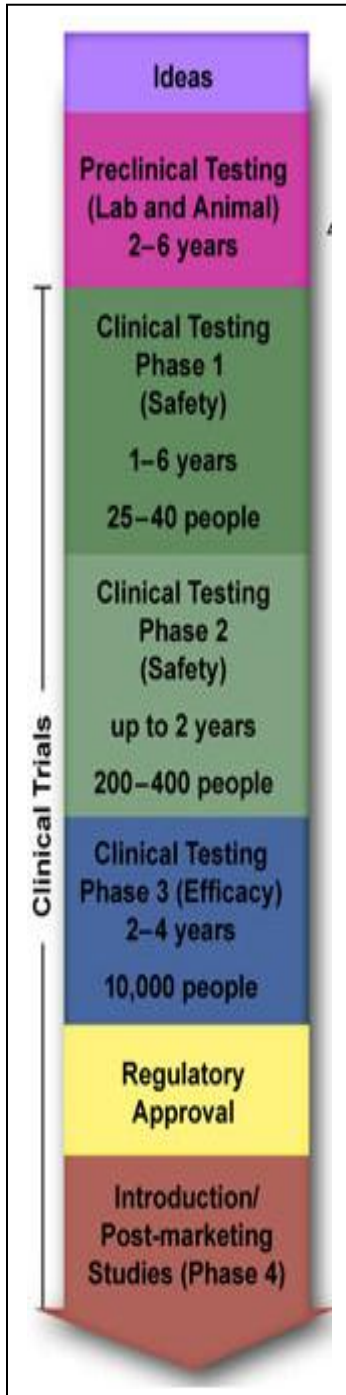
<sup>a</sup> Good Clinical Practice (GCP) is an international quality standard provided by the International Conference on Harmonisation (ICH) that governments use to guide regulations about protecting human subjects in clinical trials and assuring the safety and efficacy of new compounds. (Wikipedia, GCP, 2/20/11)

#### Ethical rationale for the *inclusion* of pregnant women in medical research

Principle	Rationale
Beneficence	Improve the health and safety of pregnant women and their babies.
Non-maleficence	Gain knowledge to evaluate risks and benefits of treatment so that you do no harm, avoid exposure of fetus with no benefit to mother, and prevent termination of wanted pregnancies due to fear.
Justice	Allow access to the best treatment available to all sectors of society equally; and follow regulations.
Autonomy	The pregnant woman has the right to decide whether to accept risk.
Good clinical practice standards	Follow currently accepted best practices and work to improve them.
Informed consent	Cannot have informed consent (balancing risks and benefits) without information.

## APPENDIX II

### The U.S. Drug Development Process



Potential new drug products (author's note: I will use the term "drug" but the process is similar for vaccines, biologics, and devices) are evaluated via computer modeling, laboratory testing, and animal studies prior to being tested on human subjects. Based on the results of these studies, the new drug's pharmaceutical company sponsor submits an application to the FDA for approval to conduct testing in human subjects. Upon approval, the first clinical use of the potential new drug product in humans occurs in Phase I studies. These studies are conducted on a small number (20-100) of healthy volunteers to ascertain the effect of the drug on a healthy person. Results may corroborate previous findings from pre-clinical (animal) testing. If results are favorable, Phase II testing is performed on subjects with the condition or disease that the potential new drug product is intended to treat.

Figure from the Global Campaign for Microbicides, [http://www.global-campaign.org/clinical\\_testing.htm](http://www.global-campaign.org/clinical_testing.htm), image available at <http://www.global-campaign.org/clientfiles/ClinicalTrials1.jpg>; accessed 09July2011.

The size of these studies varies depending on the frequency of the condition in the population but can range from 20 to 300 subjects. These tests provide information on efficacy, dosing, and safety. Finally, large clinical trials are conducted (Phase III studies) on anywhere from 300 to 3000 subjects or more, to obtain additional data about effectiveness and safety. These study results, in many cases, "aim to change medical practices, for example by comparing a new treatment with the best standard treatment."<sup>313</sup>

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<sup>313</sup>Weijer, C. (1999). Selecting subjects for participation in clinical research: One sphere of justice. *Journal of Medical Ethics*, 25, 31-36, p. 34.

## **APPENDIX III**

### **The Interview Guide**

#### **The Participation of Pregnant Women in Clinical Research: Implications for Practice within the US Pharmaceutical Industry**

##### **INTERVIEW GUIDE FOR KEY INFORMANTS IN INDUSTRY OR IRBs**

###### **Intro:**

Thank you for agreeing to speak with me. As you know, I am here to interview you about whether pregnant women can and should be included in clinical trials. I recently learned that FDA has a draft guidance in review at the agency on this topic. I also know about a group of physicians and academics who are advocating for greater inclusion. Being in industry, I wondered what our position is on the subject – or if we even have one. I found that there is little information from industry on this topic in the literature so I am exploring the subject from the industry perspective for my doctoral dissertation. I am a student in the Executive Doctoral Program in Health Leadership at the University of North Carolina at Chapel Hill Gillings School of Global Public Health.

I want to remind you that by agreeing to meet with me, you have consented to participate in this study. You may decline to participate, decline to answer any question, or stop at any time. However, your responses will be valuable to the results of this study. The information collected in this study will be kept confidential. Your specific answers will not be attributed to you or to your organization. The interview results will only be used in summary form to discuss issues related to the inclusion of pregnant women in clinical trials. With your permission, I will be both recording this interview and taking notes.

Do you have any questions? Do I have your permission to begin?

###### **Background:**

My background: I was an OB/GYN nurse practitioner before joining Merck 13 years ago to run their Pregnancy Registry program. I worked in Drug Safety for 12 years and I'm currently working in the Merck Office of Ethics.

Key Informant background: Can you tell me the position you currently hold at your company/organization? How long have you been at the company/organization? What is your background – did you come from medicine, pharmaceutical science, business, etc?



Have you worked on any issues involving pregnant women at your company or organization?  
If yes, please briefly describe:

**Level-setting background to the interview:**

There are two scenarios:

A. One is women who become pregnant during a clinical trial and

B. the other is actually enrolling pregnant women in clinical trials

I am most interested in discussing the enrollment of pregnant women and if we have time we can talk about research subjects who inadvertently become pregnant.

When we talk about pregnant women participating in a clinical trial, we can assume that it is for a therapeutic purpose not otherwise available. [*She may not have responded to other therapies or they may be contraindicated, e.g. drug allergy or resistance, etc.*] Also, we are not talking about clinical trials for pregnancy-related conditions but rather drug intervention trials for non-pregnancy-related issues that can occur in pregnant women.

**Study Questions:**

*<Study Aim (SA) #6: influence of industry in the debate>*

1. How much control do you think the industry has over whether pregnant women should be allowed to participate in trials? In your experience, who has more control over the inclusion and exclusion criteria – the sponsor or the IRB or the FDA?

Awareness *<SA #2: raise the issue>*

FDA has a new guidance draft in clearance entitled, "Pregnant Women in Clinical Trials: Scientific and Ethical Considerations." There is also a group of health care providers, ethicists, academicians, etc., called the Second Wave consortium, who are encouraging, what they call "the rational inclusion of pregnant women in clinical trials."

2. Are you aware of the FDA guidance? and Have you heard of this advocacy group?

[If no, continue. If yes, do you know if your company is doing anything in connection with this issue? If yes, describe.]

Current state: *<background information; current state>*

3. Does your company (*or IRB*), to your knowledge, have a policy about whether or not to include pregnant women in clinical studies? If yes, describe... If there is no policy, or if you are not aware of a policy, do you know what the current practices of the company (*or IRB*) are?

Rationales: *<SA #3 and #4: isolate concerns and opportunities>*

4. Can you give me 3 or 4 reasons why a Company (*or an IRB*) would **not** want to include pregnant women in clinical trials? (*barriers*)

If mention litigation: <SA #5: *pharma's perception of litigation risk*>

4.a. Do we know that allowing pregnant women in clinical trials would result in litigation or are we presuming it would?

4.b. Do you think litigation risk is higher in the clinical trial environment or in the post-marketing environment? Why/based on what?

[Interviewer notes: *If thalidomide had been tested in clinical trials, thousands of deformities would have been avoided. There are few lawsuits about birth defects uncovered in a clinical trial, even though there have been pregnant women in studies, i.e., AIDS secondary transmission trials; Gardasil trials [almost 3000 inadvertent pregnancies among 27000 women of childbearing age]. If equal risk: why do we take one risk and not the other?]*

5. Aside from studies that are specifically about conditions of pregnancy, can you give me 3 or 4 reasons why a Company (*or an IRB*) should or might want to include pregnant women in clinical trials? (*opportunities*)

Opportunities: <SA #4: *potential opportunities*>

6. If pregnant women were to be enrolled, how do you think we should do that?

- For example, wait to end of Phase III until have safety and efficacy in non-pregnant population, then enroll pregnant women?
- Other ways? (*pk studies, look at toxicity studies, other drugs in class, alternatives*)

7. If pregnant women were enrolled, what steps could be taken to safeguard the fetuses and the pregnant women who consent to participate?

8. I want to brainstorm about what it would take to have Companies open (*or IRBs approve*) relevant clinical trials to pregnant women. What do you think it would take?

- Would a guidance document be strong enough or would it need to be by regulation?
- Would Company indemnification be necessary? Is that a realistic option?
- Would patent extensions, like those implemented for pediatric trials, be a viable enticement?
- Are there other solutions or incentives you can think of?

Alternatives <SA #4: *potential opportunities*>

9. If not enrolling in clinical trials, what are alternative ways to get this information? Are there alternative study designs or data collection methods that could include pregnant women?

- Do you think a pharmaceutical company would support or fund this kind of research? Why or why not?

10. One of the challenges in doing research with pregnant women is addressing the ethical issues it raises. What ethical problems do you think are most challenging or important?"

*[Prompt: The inclusion of pregnant women in clinical trials raises questions about industry's contributions to the good of society vs our contributions to our shareholders. How do we reconcile the need for improved knowledge about how to treat pregnant women with the costs and risks to the companies?]*

11. What else should be added to this discussion about the inclusion of pregnant women in clinical research?

*[If there is time left to discuss]*

### **B. Women who become pregnant in clinical trials**

1. Does your company have a policy about what to do with women who become pregnant during a trial?

2. If no policy, what is current practice? Are they always disenrolled and followed to outcome? *[Can you name a protocol in which women who became pregnant stayed on study drug?]*

3. Can you think of a situation where a woman who becomes pregnant should remain in the study? *[e.g., when potential benefits outweigh risks of a) ongoing fetal exposure to study drug, b) risk of discontinuing maternal therapy, c) risk of exposing fetus to additional drugs if mother must go on alternative therapy.]*

4. What would be needed to retain her in the trial? *[new informed consent – discuss alt tx and comparative tx risks and benefits, incl risk of untreated maternal disease]*

Are there any other comments you'd like to add about this or any other topic?

If you would like to contact me after our discussion today, please feel free to do so. I can be reached at 267-231-7215 or at [kristine\\_shields@merck.com](mailto:kristine_shields@merck.com).

**Again, thank you so much for agreeing to this meeting. If you wish to reach me, please feel free to call me or send an email.**

**The Participation of Pregnant Women in Clinical Research:  
Implications for Practice within the US Pharmaceutical Industry**

**INTERVIEW GUIDE FOR KEY INFORMANTS AT FDA, PhRMA and BIO**

**Intro:**

Thank you for agreeing to speak with me. As you know, I am here to interview you about whether pregnant women can and should be included in clinical trials. I recently learned that FDA has a draft guidance in review at the agency on this topic. I also know about a group of physicians and academics who are advocating for greater inclusion. Being in industry, I wondered what our position is on the subject – or if we even have one. I found that there is little information from industry on this topic in the literature so I am exploring the subject from the industry perspective for my doctoral dissertation. I am a student in the Executive Doctoral Program in Health Leadership at the University of North Carolina at Chapel Hill Gillings School of Global Public Health.

I want to remind you that by agreeing to meet with me, you have consented to participate in this study. You may decline to participate, decline to answer any question, or stop at any time. However, your responses will be valuable to the results of this study. The information collected in this study will be kept confidential. Your specific answers will not be attributed to you or to your organization. The interview results will only be used in summary form to discuss issues related to the inclusion of pregnant women in clinical trials. I will be both recording this interview and taking notes.

Do you have any questions? Do I have your permission to begin?

**Background:**

My background: I was an OB/GYN nurse practitioner before joining Merck 13 years ago to run their Pregnancy Registry program. I worked in Drug Safety for 12 years and I'm currently working in the Merck Office of Ethics.

Key Informant background: Can you tell me the position you currently hold at FDA/PhRMA? How long have you been at the organization?

What is your background – did you come from medicine, pharmaceutical science, business, etc?

Do you now or have you worked on any issues involving pregnant women at FDA/PhRMA? If yes, please briefly describe:

## **Level-setting background to the interview:**

There are two scenarios:

A. One is women who become pregnant during a clinical trial and

B. the other is actually enrolling pregnant women in clinical trials

I am most interested in discussing the enrollment of pregnant women and if we have time we can talk about research subjects who inadvertently become pregnant.

When we talk about pregnant women participating in a clinical trial, we can assume that it is for a therapeutic purpose not otherwise available. [*She may not have responded to other therapies or they may be contraindicated, e.g. drug allergy or resistance, etc.*] Also, we are not talking about clinical trials for pregnancy-related conditions but rather drug intervention trials for non-pregnancy-related issues that can occur in pregnant women.

## **Study Questions:**

<SA #6: *influence of industry in the debate*>

1. How much control do you think the industry has over whether pregnant women should be allowed to participate in trials? In your experience, who has more control over the inclusion and exclusion criteria – the sponsor or the IRB or the FDA?

Awareness <SA #2: *raise the issue*>

FDA has a new guidance draft in clearance entitled, "Pregnant Women in Clinical Trials: Scientific and Ethical Considerations." There is also a group of health care providers, ethicists, academicians, etc., called the Second Wave Consortium, who are encouraging, what they call "the rational inclusion of pregnant women in clinical trials."

2P. For PhRMA rep: Are you aware of the new FDA draft guidance entitled, "Pregnant Women in Clinical Trials: Scientific and Ethical Consideration"? Was it influenced by PhRMA? [*If yes, describe, if No continue:*] Is PhRMA doing anything in connection with this issue? If yes, describe.]

Are you aware of the Second Wave advocacy group? [*If yes, describe, if No continue:*]

2F. For FDA rep: What is your involvement with the guidance document? What is your opinion of the guidance? What is your opinion of how the industry will respond to the proposals in the guidance?

Are you aware of the Second Wave advocacy group? [*If yes, describe, if No continue:*]

## **A. Enrolling pregnant women in clinical trials**

Current state: <*background information; current state*>

3. Do most companies, to your knowledge, have a policy about whether or not to include pregnant women in clinical studies? If yes, describe... If there is no policy, or if you are not aware of a policy, do you know what the current practices of most companies are?

Rationales: <SA #3 and #4: isolate concerns and opportunities>

4. Can you give me 3 or 4 reasons why a Company would not want to include pregnant women in clinical trials?

If don't mention litigation, raise the issue, if mention litigation: <SA #5: pharma's perception of litigation risk>

4.a. Do we know that allowing pregnant women in clinical trials would result in litigation or are we presuming it would?

4.b. Do you think litigation risk is higher in the clinical trial environment or in the post-marketing environment? Why/based on what?

[Interviewer notes: *If thalidomide had been tested in clinical trials, thousands of deformities would have been avoided. There are few lawsuits that arose over birth defects uncovered in a clinical trial, even though there have been pregnant women in studies, i.e., AIDS secondary transmission trials; Gardasil trials [almost 3000 inadvertent pregnancies among 27000 women of childbearing age]. If equal risk: why do we take one risk and not the other?*]

5. Aside from studies that are specifically about conditions of pregnancy, can you give me 3 or 4 reasons why a Company might **want** to include pregnant women in clinical trials?

Opportunities: <SA #4: potential opportunities>

6. If pregnant women were to be enrolled, how do you think we should do that?

- For example, wait to end of Phase III until have safety and efficacy in non-pregnant population, then enroll pregnant women?
- Other ways? (*pk studies, look at toxicity studies, other drugs in class, alternatives*)

7. If pregnant women were enrolled, what steps could be taken to safeguard the fetuses and the pregnant women who consent to participate?

8. I want to brainstorm about what it would take to have Companies open relevant clinical trials to pregnant women. What do you think it would take?

8a. Would a guidance document be strong enough or would it need to be by regulation?

8b. Would Company indemnification be necessary?

8c. Would patent extensions, like those implemented for pediatric trials, be a viable solution?

8d. Are there other solutions?

Alternatives <SA #4: potential opportunities>

9. If not enrolling in clinical trials, what are alternative ways to get this information? Are there alternative study designs or data collection methods that could include pregnant women?

9a. Do you think a pharmaceutical company would support or fund this kind of research? Why or why not?

10. One of the challenges in doing research with pregnant women is addressing the ethical issues it raises. What ethical problems do you think are most challenging or important?"

11. What else should be added to this discussion about the inclusion of pregnant women in clinical research?

*[If there is time left to discuss]*

**B. Women who become pregnant in clinical trials**

1. So, first, do you know if companies have policies about what to do with women who become pregnant during a trial? If yes, describe:

2. If no (or no policy), what is their current practice? Are pregnant women always disenrolled and followed to outcome? [Can you name a protocol in which women who became pregnant stayed on study drug?]

3. Can you think of situations where it would be appropriate for a woman who becomes pregnant to remain in the study? [*when potential benefits outweigh risks of a) ongoing fetal exposure to study drug, b) risk of discontinuing maternal therapy, c) risk of exposing fetus to additional drugs if mother must go on alternative therapy.*]

4. What would be needed to retain her in the trial? [new informed consent – discuss alt tx and comparative tx risks and benefits, incl risk of untreated maternal disease]

**Again, thank you so much for agreeing to this meeting. If you wish to reach me, please feel free to call me or send an email.**

**Study Aims (SA):**

1. Quantify the frequency of the participation of pregnant women in current pharmaceutical company-based studies by accessing the inclusion and exclusion criteria via ClinicalTrials.gov. (The Food and Drug Modernization Act of 2007 mandates that all federally and privately funded clinical trials be posted on the NIH website, ClinicalTrials.gov.)
2. Raise the issue to selected pharmaceutical industry representatives and related organizations to heighten their awareness of the issue and the debate.
3. Isolate the concerns of the pharmaceutical industry representatives about including pregnant women in clinical trials to further our understanding of potential barriers to their inclusion.
4. Isolate potential opportunities for inclusion of pregnant women in clinical trials from the pharmaceutical industry representatives' perspectives.
5. Ascertain the pharmaceutical industry and related organizations' representatives' perceptions of litigation risk [regarding how influential it is and is it a real risk?]. (This is one of two key pieces of missing information identified by the Second Wave Consortium workshop.)<sup>314</sup>
6. Explore the selected pharmaceutical industry and related organization representatives' perspective about the industry's role in affecting the outcome of the debate [how influential is it?](This is the second key piece of missing information identified by the Second Wave Consortium workshop.)<sup>315</sup>

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<sup>314</sup> Personal communication, AD Lyerly, 12Nov2010.

<sup>315</sup> Personal communication, AD Lyerly, 12Nov2010.



## APPENDIX IV

### QUALITATIVE STUDY RESULTS

#### Key Findings from Key Informant Interviews

##### Question

##### Key Findings

**1 Who has the most control over whether pregnant women are included in clinical trials – the pharmaceutical company sponsor, the Institutional Review Board (IRB), or the FDA?**

1a. Four stakeholders were identified as having the power to veto a clinical trial: the trial's sponsor, the FDA, the IRB, and the institution at which the trial is to take place.

1b. The Sponsor was perceived to have the most control over whether or not pregnant women were included as study subjects. Without proposing their inclusion, it was unlikely that the FDA or IRB would suggest it. In addition, it was felt that because the company would have the highest risk for liability, they had the right to be the decision-makers.

1c. FDA was found to have the least influence as there is no regulatory statute that requires their exclusion.

1d. IRBs were felt to be a potential barrier to inclusion based on their cautious nature, their patient-centric focus, and the variability of decisions from one IRB to the next.

1e. All of these stakeholders were perceived to be resistant to the idea of including pregnant women in clinical trials.

**2 Are you aware of the FDA Guidance? Have you heard of the Second Wave advocacy group?**

2a. There is a lack of awareness among industry employees and within related organizations about the issue of the inclusion of pregnant women in clinical trials, about the impending release of an FDA guidance document on the topic, and about the Second Wave Coalition advocacy group. The interviewees implied there is also a lack of awareness of the issue among the general public. The implication of this dearth of awareness at all levels was seen to be a potential barrier to the initiation of change and a facilitator of the status quo.

2b. It is critical to get the issue into the public domain in order to change current thinking and get stakeholders involved. The work of the Second Wave Consortium was important in this regard.

2c. There is opportunity for change utilizing the government's and public's current interest in protection against bioterrorism.

2d. There is opportunity for change utilizing the work that has been done in clinical trials for HIV treatment and the prevention of vertical transmission.

2e. There exist similarities between the exclusion of pregnant women from clinical research and the former exclusion of pediatric patients from clinical research. There may be lessons learned from the endeavors of the pediatric sector that have resulted in mandated pediatric clinical studies.

**3 Does your organization have a policy about whether or not to include pregnant women in clinical studies? What are the current practices there?**

3a. Most companies exclude pregnant women from their studies.

3b. IRBs generally have policies regarding the inclusion of pregnant women in clinical studies, based on the Code of Federal Regulations regarding vulnerable populations. They feel that their policies could be improved by an FDA guidance on this topic.

3c. Some companies have experience doing clinical studies that include pregnant women. Information on drug safety gathered from other sources can be helpful in setting up clinical studies for pregnant women. Some women who become pregnant while enrolled in clinical studies may remain in some studies on an ad hoc, compassionate use basis.

3d. FDA feels that studies should be done for certain products where the need is well established.

**4 Can you give me 3 or 4 reasons why a company or organization would not want to include pregnant women in clinical trials?**

4a. The fear of causing harm to a fetus is the most important concern limiting the inclusion of pregnant women in clinical trials.

4b. The fear of litigation is one of the major concerns that is limiting the inclusion of pregnant women in clinical trials.

4c. The efficacy, safety, and proper dose of a medication must be known

to some extent prior to testing the drug in pregnant women.

4d. Industry has little experience designing clinical trials that include pregnant women. More information is needed to assist with the design of such studies.

4e. National and international regulations regarding the inclusion of pregnant women in clinical studies are not well understood.

4f. Studying drugs in pregnant women would provide valuable information for the label, which would improve the treatment of pregnant women.

4g. Industry is reluctant to risk the approval of a drug for the non-pregnant population or the reputation of its company by testing drugs on pregnant women.

4h. A sufficient number of pregnant women must be included in a study of pregnant women to ensure that the data collected is interpretable.

4i. Industry perceives little motivation or advocacy for the study of its products in pregnant women.

**4a Do we know that allowing pregnant women in clinical trials would result in litigation or are we presuming it would?**

4a1. Because we have little actual experience, we presume, but don't know, that the litigation risks would be higher in clinical trials of pregnant women than in clinical trials in general.

4a2. There is a perceived risk that excluding pregnant women from clinical research could result in litigation due to adverse pregnancy outcomes caused by restricting pregnant women from getting the drug they needed, or caused by a drug that was not fully evaluated was put on the market.

4a3. Thorough informed consent, complete disclosure in the Investigator's Brochure, FDA approval, IRB review, risk minimization, and the disclosure that the trial is intended to help pregnant women now and in the future, could help protect the company from lawsuits in clinical trials of pregnant women.

4a4. Our litigious society, the emotional component in jury trials, and increased litigation risk in the obstetrical community could increase the risk of litigation in clinical trials of pregnant women.

4a5. The risk of liability for injuries that occur during research in general is low.

4a6. Some respondents believed that the increased litigation risk would be minimal and should not be a deciding factor in whether or not to conduct trials in pregnant women.

**4b Do you think litigation is higher in the clinical trial environment or in the post-marketing environment?**

4b1. Pharmaceutical companies are concerned about litigation risks associated with testing products on pregnant women in both the clinical trial and the post-marketing environment.

4b2. Fear of litigation may be deterring pharmaceutical companies from testing drugs in pregnant women in clinical trials.

4b3. Fear of litigation about birth defects may be deterring the development of potential pharmaceutical interventions that address unmet medical needs of the population.

4b4. Evaluating the safety of drug in pregnant women may increase a company's risk for litigation.

4b5. The risk of litigation is considered to be higher in the post-marketing environment than in the clinical trial setting.

**5 Aside from studies that are specifically about conditions of pregnancy, can you give me 3 or 4 reasons why a company (or an IRB) should or might want to include pregnant women in clinical trials?**

5a. Members of pharmaceutical companies, IRBs, PhRMA, and FDA, physicians, lawyers, and business people, agree that there are compelling reasons to conduct clinical trials in pregnant patients based on the need for information on how to treat them effectively.

5b. Conducting trials on drug treatments for pregnant women is advantageous for the pregnant women, the health care providers, the prescribers, the FDA, the pharmaceutical company, and society in general.

5c. Pregnant women are at a higher risk if clinical trials are not conducted than if they are conducted.

**6 If pregnant women were to be enrolled, how do you think we should do that?**

6a. We are already doing clinical trials in pregnant women. Building upon this experience, we can start evaluate many more drugs that are or will be used by pregnant women to treat their medical conditions.

6b. There are new advances being made to evaluate potential drug therapies in the preclinical area that will help to identify therapies that are appropriate for testing in pregnant women and to monitor the therapies being tested.

6c. There are manageable ways to design studies that minimize risk to pregnant women, their pregnancies, and their fetuses.

6d. Planning for drug testing in pregnant women should be part of the routine drug development process. Evaluation of the drug's use in pregnancy should continue after the drug is marketed and be ongoing through the lifetime of the product.

**7 If pregnant women were enrolled, what steps could be taken to safeguard the fetuses and the pregnant women who consent to participate?**

7a. Data collection and analysis should be applied in an iterative fashion so that each pregnant patient entering a study should benefit from the knowledge gained from every patient that has gone before her.

7b. A pregnancy-specific independent data safety monitoring board should provide oversight and decision-making functions.

**8 What would it take to have companies open (or IRBs approve) relevant clinical trials to pregnant women? Would a guidance document be strong enough or would it need to be by regulation?**

8a. The subjects in this study believe that it would take much work on the part of many stakeholders for pregnant women to participate in clinical research.

8b. Most of the subjects believe that a guidance document from FDA on the topic of including pregnant women in clinical trials will increase awareness and discussion within and outside of the pharmaceutical companies, but that it may not be enough to cause a change in current practices.

8c. Company indemnification should be included when considering all the

potential solutions to improving knowledge of pharmaceutical therapy for pregnant women.

8d. Patent extensions and transferable extensions should be considered cautiously due to negative industry and public perception.

8e. Stakeholders within and external to the pharmaceutical industry have suggestions on how to improve the inclusion of pregnant women in clinical research.

**9 If not enrolling in clinical trials, what are alternative ways to get this information? A. Are there alternative study designs or data collection methods that could include pregnant women? B. Do you think a pharmaceutical company would support or fund this kind of research?**

9a. There are opportunities to improve our knowledge of the efficacy and safety of medication use in pregnancy in pre-clinical techniques and analysis, in inadvertent pregnancy exposures during clinical trials, and in post-marketing surveillance, pregnancy registries, and epidemiologic studies. Current methodologies could be improved and new methodologies should be explored.

9b. Regulatory agency support would be helpful to these efforts including the release of the pregnancy labeling rule, the guidance on inclusion of pregnant women in clinical research, and agency recommendations on the analysis of pregnancy data.

9c. Pharmaceutical support and funding for the collection and analysis of use-in-pregnancy data would be helped by an articulated medical and societal perception of need and by regulatory agency pressure.

**10 One of the challenges in doing research with pregnant women is addressing the ethical issues it raises. What ethical problems do you think are most challenging or important?**

10a. Study participants cited ethical principles to both justify and condemn the exclusion of pregnant women from clinical research including non-maleficence, autonomy, and justice and suggested that feminist ethics might make a contribution to the topic.

10b. Informed consent was considered to be an important issue on two counts: 1) that a pregnant woman has the opportunity to be given informed consent (distributive justice) and that the document is complete, honest, and comprehensible; and 2) that the fetus be considered to have an interest in the decision to participate in the study.

10c. The issue of including pregnant women in clinical research implicitly raises issues of fetal rights, abortion, and divergent perceptions of the fetus in society.

10d. While most participants felt that pharmaceutical companies had a responsibility to provide safety information for products that would be used by pregnant women, many also acknowledged that business decisions might decide whether research in this area would be conducted. The attitude of senior management and regulatory agency guidance were recognized as factors that could influence the decision.

## APPENDIX V

### The Plan for Change

<b>Plan #</b>	<b>Goal</b>	<b>Target</b>	<b>Intervention</b>
<b>1</b>	Increase <b>awareness of the current practice</b> of including pregnant women in, or excluding them from, clinical research	Industry, Stakeholders, General Public	Published paper on extent of exclusion in scientific literature
<b>2</b>	Increase <b>awareness of the 'issue as a problem'</b> among individuals in industry, IRBs, and industry associations	Industry colleagues, Senior management	White Paper to key informants, PhRMA and BIO; Conference presentations
<b>3</b>	Provision of <b>potential solutions for industry</b> consideration in guidance responses & internal policies	Industry colleagues, Senior management	White Paper to FDA, PhRMA, BIO, and companies
<b>4</b>	Provision of <b>potential solutions for companies'</b> draft response	Company colleagues & senior management	Participate in drafting my company's response to FDA
<b>5</b>	<b>Industry perspective included</b> in discussion of the issue	FDA, Stakeholders, Public	Present study findings at FDA hearing, if applicable
<b>6</b>	Increased knowledge of <b>issue in public domain</b>	Advocates, Academia, General public	Additional publications and presentations
<b>7</b>	<b>Personal influence on companies'</b> internal deliberations on issue	Company colleagues & senior management	Continue involvement in issue at my company
<b>8</b>	Issue remains in public and professional consciousness; <b>continued advocacy</b> for increased evidence-based treatment for pregnant women	Second Wave Consortium, PhRMA, other organizations	Continue involvement in issue in other organizations



**APPENDIX VI**

**The Inclusion of Pregnant Women in Clinical Research:  
Implications for the U.S. Pharmaceutical Industry**

**A White Paper**

**June 2012**

**Kristine Shields MSN, DrPH  
University of North Carolina  
Gillings School of Global Public Health**

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## 1. Introduction

The treatment of medical conditions complicating pregnancy is challenged by a serious lack of information about the safety and effectiveness of the medications used by pregnant women. To improve our knowledge of what constitutes the most effective therapeutic interventions, we conduct systematic research. Research for pregnant women, however, is challenging. One study found that, of 368 Phase IV studies in which pregnant women could appropriately participate (the drugs were in FDA pregnancy categories A, B, or C and the conditions being studied could occur during pregnancy), 94% excluded pregnant women from enrollment.<sup>(1)</sup> (See Addendum I.) Stakeholders like the Second Wave Consortium<sup>a</sup> <sup>(2)</sup> are advocating for increased inclusion. In response, the U.S. Food and Drug Administration (FDA) will release a draft guidance in 2012 entitled, "Pregnant Women in Clinical Research: Scientific and Ethical Considerations." This white paper provides data from key informant interviews with industry researchers and lawyers, Institutional Review Board (IRB) members, and representatives from FDA and the industry association (the Pharmaceutical Research and Manufacturers of America [PhRMA]) <sup>(1)</sup><sup>b</sup>, to assist industry as it prepares a considered response to the FDA's call for comment.

## 2. Background

In the U.S., more than a third of the 1.7 million women who give birth each year experience some type of adverse complication <sup>(3)</sup> and two women die every day from pregnancy-related causes.<sup>(4)</sup> To treat the morbidity, prevent the mortality, and achieve the optimal pregnancy outcome, over 60 percent of pregnant women are prescribed one or more drugs <sup>(5,6)</sup>.

Because pregnant women are largely excluded from participation in clinical research studies,

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<sup>a</sup> The Second Wave Consortium is "a consortium of physicians, scientists, and bioethicists working to advocate for the importance of advancing the evidence base for the treatment of pregnant women facing serious illness."

<sup>b</sup> Via key informant interviews, the study, conducted in 2011-2, sought to isolate the perspectives of industry and related organizations about pregnant women and clinical research. Participants included research, regulatory, and safety staff from pharmaceutical (n=5) and biotech (n=3) companies, legal counsel from industry (n=2), an IRB (n=1) and PhRMA (n=1), and other representatives from PhRMA (n=1), IRBs (n=2), and FDA (n=1).

the efficacy and safety of these medications when used during pregnancy are largely unknown.(7)

The potential impact of a lack of data for drug efficacy during pregnancy is illustrated by the 2002 recommendation by the American College of Obstetricians and Gynecologists (ACOG) of the use of amoxicillin by pregnant women for anthrax post-exposure prophylaxis. Subsequent study results, published in 2007, showed that the dosage regimen was ineffective for the treatment of pregnant and post-partum women.(8) No studies are available for ciprofloxacin or doxycycline, the alternative antibiotics. Women's health care providers lament that the "current evidence base for the care of pregnant women facing illness is widely regarded as deplorable."(9)

The exclusion of pregnant women from participation in drug studies is widely accepted as the right thing to do. Thalidomide casts a long shadow.<sup>c</sup> Unless you are a pregnant woman with an illness or her health care provider, the consequences of the lack of research results are largely invisible.

Interviews with key informants in industry, IRBs, PhRMA, and FDA found that the exclusion of pregnant women from clinical research is primarily based on the ethical principle of beneficence - the desire to avoid causing harm to a fetus. Even when the negative consequences are recognized, other motives for their exclusion may be difficult to overcome. These include the perceived risk of litigation, scientific validity issues, risks to drug approval and to company reputation, and the increased complexity of conducting such trials. The lack of advocacy for their inclusion, the lack of a regulatory requirement or recommendation, and historic precedent are other rationales.

The FDA (10), the Institute of Medicine (11), the Council for International Organizations of Medical Sciences (CIOMS) (12), and ACOG (13) recommend the inclusion of pregnant

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<sup>c</sup> In the late 1950s and 1960s, women around the world were prescribed thalidomide to prevent miscarriage, for hyperemesis, and for sedation. It took several years, and over 10,000 cases of severe limb defects (phocomelia), before its teratogenic properties were recognized.

women in research when the benefits outweigh the risks. These recommendations and an increase in requests to review clinical protocols that included pregnant women, spurred FDA's development of the guidance document. "Pregnant Women in Clinical Research: Scientific and Ethical Considerations"(14) is currently in review at the agency and slated for release in 2012. It will challenge the industry to increase its inclusion of pregnant women in clinical research studies. This White Paper presents research results to inform industry of the anticipated recommendations and potential responses to the call for comment following the release of the guidance.

### **3. Anticipated content of the draft guidance**

It is anticipated that the FDA draft guidance will present the following **rationale** for the increased inclusion of pregnant women in clinical research (1,15):

**Why** should pregnant women be included in clinical research?

- Controlled studies provide evidence-based guidance on treatment options for application in medically compromised pregnancies.
- The supervision of the patient and the quality of the data acquired in rigorous controlled studies is superior to that received in the post-marketing environment.
- Safety and efficacy information will be obtained sooner and with fewer pregnant women and fetuses exposed than if the drug information is obtained following its release on the market (recognizing, as with all drugs, that some objectives cannot be met until widespread use occurs).

**When** should pregnant women participate in clinical research?

When their exclusion cannot be justified by scientific rationale:

- When participation in a study provides therapeutic benefit and the anticipated benefits exceed the anticipated risks
- When there is medical need to treat a particular pregnant woman or pregnant women in general and there is reliable information from animal testing or human experience on the teratogenic and developmental risks of the proposed treatment

It is anticipated that the FDA draft guidance will present the following **recommendations** for the increased inclusion of pregnant women in clinical research:

**Where** in drug development should research include pregnant women?

- Clinical environment:
  - Pharmacokinetic (PK) testing
  - End of Phase III studies designed to include pregnant women
- Post-marketing:
  - Phase IV clinical studies designed for pregnant women
  - Enhanced surveillance: pregnancy exposure registries for active surveillance, cohort and case control studies for signal evaluation

**What** pregnant women should be included in clinical research?

- Pregnant women in need of treatment (whether for pregnancy-related conditions or unrelated illness) can be enrolled:
  - in studies that potentially provide therapeutic benefit and whose potential benefits exceed the potential risks
  - in studies designed to evaluate safety and/or efficacy during pregnancy
  - in general clinical trials on a compassionate use basis after individual consideration of risk/benefit and re-consent
- Pregnant women already taking approved medications in the post-marketing environment
- Women who become pregnant during a clinical trial who desire to remain in the study after individual consideration of risk/benefit and re-consent
  - Factors for consideration include the risk to the pregnant woman and her fetus from continuation of therapy, discontinuation of therapy, and the effectiveness and risks of alternative therapies (including risk of fetal exposure to the experimental *and* the alternative therapy).

## 4. Considerations for industry response to FDA draft guidance

When engaged in dialogue on this issue, individuals within pharmaceutical companies and IRBs, including their legal counsel, recognized the unintended adverse consequences of pregnant women's exclusion from clinical research. While understanding the need for change from the current practice of general exclusion, they cautioned that change would be difficult and probably incremental (1). Via the key informant interviews, experts on clinical trial design and conduct identified barriers to inclusion and provided potential solutions to the concerns. These are presented in Table 1 and are further discussed below.

**Table 1. Concerns and Solutions identified by Industry Informants**

Key Concerns	Key Potential Solutions
Causing harm to the fetus; Scientific concerns	Study design; scientific advances in modeling and animal testing; end of Phase III and post-marketing studies
Litigation	Guidance/regulation; informed consent; indemnification; improved awareness of issue in public domain
Enrollment concerns	PK testing on small numbers; partnerships with OPRU* and obstetrical community, data from multiple sources
Negative impact on initial approval	Post-approval studies
Lack of regulatory agency support, unclear regulations	FDA guidance document, international harmonization
Business concerns	Define market; conduct post-approval studies; devise incentives and protections
Lack of experience and know-how	Collaboration, best practices, innovation, science

\*see pg 8 for description of OPRUs

### Attitudes towards inclusion:

- Change from the widespread practice of excluding pregnant women from clinical research studies will call for regulatory **directives**, financial **incentives**, and legal **protections**.
- Pharmaceutical companies have a responsibility to provide efficacy and safety information for products **intended for women of childbearing potential**. Prioritizing studies for pregnant women by those conditions and drug classes where the need is greatest may facilitate acceptance and target resources to where they are needed the most.
- Consideration of the need for drug testing in pregnant women should be part of **routine drug development** for all new molecular entities.

- Evaluation of all products' effects on pregnancy should continue after the drugs are marketed and be **ongoing** through the lifetime of the product.

### **Clinical concerns: Efficacy and Safety**

- Clinical studies can be designed to minimize risk. **Build on the experience** we have gained from prior studies in pregnant women, e.g., studies in HIV transmission, to plan future studies.
- Data collection and analysis should be applied in an **iterative** fashion so that each pregnant patient entering a study should **benefit** from the knowledge gained from every patient that has gone before her.
- **All** pregnancies that occur during clinical trials should be **followed to outcome**.
- Consider **retaining** women who inadvertently become pregnant during clinical trials following an individual benefit/risk assessment and re-consent. Consider the risk of the exposure vs. the benefit of the treatment, the risk of discontinuing treatment, the efficacy and safety - including fetal exposure – of the alternative treatments.

### **Efficacy**

- Key informants recommended that a treatment's **efficacy should be confirmed** by completing clinical trials in men and non-pregnant women **before initiating testing in pregnant women**.
- Proper dosing for pregnant women can only be gained by conducting PK testing in pregnant women. Such testing can be done on small numbers of women, and could be done with pregnant women **who are already taking the approved medication** in post-approval studies.
- Since 2004, four Obstetric-Fetal Pharmacology Research Units (OPRUs) have been receiving government funding to conduct pharmacology studies on pregnant women "to enhance understanding of obstetrical pharmacokinetics and pharmacodynamics, and improve appropriate therapeutics during pregnancy"(16). Pregnancy-induced changes in PK and PD have been documented (16). Sponsors should **partner** with the OPRUs to conduct studies that determine correct dosing for pregnant women.



## Safety

- We can improve our knowledge of the safety of medication in pregnancy by **innovation in pre-clinical** techniques and analysis, by systematic learning from **inadvertent pregnancy exposures** during clinical trials, in **planned trials** for pregnant women, and in **post-marketing** surveillance, pregnancy registries, and epidemiologic studies.
- Some knowledge of a drug's safety in pregnancy can be obtained from doing careful testing in **animals**. Acknowledging the need to be extremely cautious, it is important to note that the majority of drugs are not teratogenic, and all but one<sup>d</sup> of the drugs known to be teratogenic in humans are teratogenic in animals as well (17). Current advances in drug modeling, Phase 0 testing, and advancements in animal testing are **innovations** being made by **pre-clinical** scientists.
- Once efficacy in non-pregnant subjects and PK parameters in pregnant women have been established, studies can be designed specifically for the enrollment of pregnant women in late Phase III and Phase IV.

For FDA consideration: If the potential therapeutic benefit to the pregnant woman (and fetus) exceeds the risk of including her in a clinical study, then there is no scientific justification for her exclusion. At what point does the agency consider that the Sponsor has 'enough' pre-clinical and clinical data to perform a benefit/risk assessment? What constitutes adequate data? Is there agency guidance on the evaluation of pregnancy exposure data on this point? The establishment of best practices for data collection and evaluation can provide standardization, improved knowledge, and protection from litigation.

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<sup>d</sup> Misoprostol is the exception.

## Company Oversight

- Companies should have **internal women's health committees** composed of subject matter experts within the company to consult on pregnancy-related issues – in study design and planning, in policy making on inclusion and retention in trials, in post-approval activities and Risk Evaluation and Mitigation Strategies.
- An **independent pregnancy-specific data safety monitoring board** should provide oversight and decision-making functions for open trials, similar to other organ-specific DSMBs.

## Business concerns

Aside from safety issues, valid business concerns must be recognized and addressed before change can be considered. These include: the additional **time** and financial **costs** with little **return on investment**, potential **delays** and threats to product approval, **litigation** risks – both **financial and reputational**.

- Business decisions will influence whether research for pregnant women will be conducted. The attitude of **senior management** and regulatory agency guidance are recognized as factors that will influence the inclusion/exclusion decision.
- Business analyses would be helpful to define the **market** for pharmaceutical use in pregnant women
- To avoid delayed initial approval and access to products with established therapeutic benefit for the general population, consider the conduct **post-approval studies** in pregnant women.

## Litigation

- There is no evidence that suggests that designing clinical trials for pregnant women will increase the **risk of litigation** against the company (though experience is limited).
- There is evidence that discovering **teratogenicity** post-marketing in therapies not evaluated during development raises the risk for litigation (18).

- Sponsors should not be punished for following best practices to ascertain if a product is teratogenic. The financial and reputational costs of a product that has been inaccurately branded teratogenic, e.g., Bendectin,<sup>°</sup> (19,20) can be substantial. Therefore, **best practices** should be defined and standardized and company **indemnification** should be considered as protections against litigation. (See further discussion of indemnification in Addendum II.)

For PhRMA consideration: Consider sponsoring the collection of additional data that would be helpful to industry to inform its response to the draft guidance including:

- **Market analysis** – what are the expected financial returns – or lack thereof – for the approved or off-label use of a product during pregnancy? What are the expected costs of conducting additional clinical trials for pregnant women? While financial considerations may not be the deciding factors in the decision to conduct such studies, the associated costs must be factored into the total research costs of a product in development.
- **Legal analysis** on the risk of increased litigation if pregnant women are:
  - retained in clinical trials in which they inadvertently became pregnant
  - included in clinical trials designed for testing in pregnancy during development (late Phase III) or in the post-marketing environment
- **Legal opinion** on potential **protections** to prevent litigation in clinical and post-marketing environment, including indemnification.

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<sup>°</sup> Bendectin, a combination of vitamin B6 and an antihistamine, which are both available over the counter as separate medications, was approved and is effective for the treatment of nausea and vomiting during pregnancy. Despite having been extensively studied in animal, clinical, and epidemiologic studies with no findings of measureable risk to the developing fetus, the product was withdrawn from the market in 1983 due solely to the burdens of litigation. The product remains on the market in the UK and Canada where it is widely used.

## Regulatory

A guidance document from FDA on the topic of including pregnant women in clinical trials will increase awareness and discussion within and outside of the pharmaceutical companies, but it may not be enough to cause a change in current practices.

- Regulatory agency measures that would promote change include:
  - the release of the Pregnancy Labeling Rule which will enhance the communication of use-in-pregnancy information in the **product label**
  - the release of the draft guidance on Pregnant Women in Clinical Research
  - agency recommendations on the **standardized analysis** of pregnancy exposure data
- The ability for Sponsors to access FDA reviewers to discuss study design options and obtain agency advice was cited as an obstacle to drug development. **Communication** between FDA reviewers and company representatives needs to be substantially improved in order to facilitate the planning and conduct of studies in pregnant women. Without communication, the voluntary conduct of such studies will be negatively impacted.
- **International harmonization** with CIOMS and the International Committee on Harmonization would assist global standardization in the current environment where many clinical studies are multinational.

## Incentives and Protections

- **Patent protections** (including transferable extensions), while helpful, should be considered but caution should be exercised due to poor industry experience with their value and negative public and political perceptions.
- Would a drug's indication for use in pregnancy, due to the small market, qualify the product for **orphan drug status**? The number of pregnant women being treated for many conditions may be <200,000.
- Consider **tax** incentives, research **subsidies**, **partnerships** with government bodies (e.g., NIH, OPRU sites), **grants**, etc.
- Consider **fast track review** for New Drug Applications that include plans for studies in pregnancy

[See Addendum II for commentary on **company indemnification**.]

## **5. Proposed Industry Response to FDA draft guidance**

Proposed recommendations from industry key informants to the FDA "Call for Comment" on its draft guidance, "Pregnant Women in Clinical Studies: Scientific and Ethical Considerations":

### **Pharmaceutical companies should consider:**

- Participating in dialogue with stakeholders about increasing the inclusion of pregnant women in clinical studies.
- Designing studies for pregnant women, on an individual product basis, including PK studies, pre- and post-approval safety and efficacy studies, pregnancy registries, and other methodologies to improve its contribution to best practices for the treatment of pregnant women with medically compromised pregnancies.
- Establishing a policy for including pregnant women in clinical development and post-marketing studies, and retaining women who inadvertently become pregnant in clinical studies if the benefits outweigh the risks and the woman requests and consents to continue to participate.

### **PhRMA should consider:**

- Producing a position paper for industry on the inclusion of pregnant women in clinical research.
- Convening a maternal health working group to consider recommendations for the expansion of the inclusion of pregnant women in clinical research.
- Sponsoring legal and market analyses to inform deliberations on the topic.

## **6. Proposed FDA actions to support industry's enrollment of pregnant women in clinical research**

Proposed recommendations from industry key informants to the FDA on its draft guidance, "Pregnant Women in Clinical Studies: Scientific and Ethical Considerations":

## **FDA should consider:**

- Identifying diseases and drug classes that are a priority for drug testing for pregnant women; prioritizing these disease and drug categories for studies in pregnant women so that resources can be targeted efficiently.
- Defining the conditions under which Sponsors should consider studies for pregnant women, e.g., prevalence of the condition in pregnancy, risk of no or delayed treatment, safety and efficacy data available for alternative treatments, etc.
- Providing a list of considerations that would result in the exclusion of pregnant women, e.g. evidence of teratogenicity in preclinical studies or human exposures, conditions that would never or rarely occur in pregnant women, treatment of the condition could usually be postponed until the conclusion of the pregnancy, etc.
- Defining the considerations that would support the inclusion of pregnant women in clinical studies, e.g., when the benefit outweighs the risk, when there is no evidence of teratogenicity in preclinical studies or human exposures, the condition commonly (define commonly) occurs in pregnant women and its treatment should not be postponed, etc.
- Developing an efficient process within the agency for *individual* review of New Drug Applications (NDAs) as to whether they should or should not include testing in pregnant women (i.e., do not recommend testing in pregnant women solely by indication and drug class).
- Identifying potential company incentives for the design and implementation of studies that include pregnant women. Consider:
  - Fast track review for NDAs that include plans for studies in pregnancy
  - Providing financial incentives to offset costs (patent protections, tax incentives, orphan drug status, research subsidization, new incentives)
  - Partnerships with NIH, CDC, OPRUs, and others to conduct studies in pregnancy
- Recommending that generic companies, where applicable, participate in and contribute to the costs of research on marketed, off-patent products used by pregnant women.

## **Future Steps**

## **Dialogue and Communication**

PhRMA, and FDA, and Industry should consider sponsoring a series of workshops to bring together key stakeholders, including the Second Wave Consortium (2), professional associations like ACOG and the March of Dimes, women's health advocates, etc., to share concerns, discuss issues, and generate and evaluate potential solutions. Understanding each other's genuine concerns and the guidance's potential impacts will be key to finding solutions. The realization of a comprehensive guidance document that addresses stakeholders' perceptions and concerns and results in acceptance of the outcome will rely upon dialogue, negotiation, and cooperation.

## **Evaluation**

The three major stakeholders, PhRMA, industry, and FDA, will need to monitor and evaluate the impact of the final guidance on the inclusion of pregnant women in clinical research.

- The evaluation of the guidance's impact on the inclusion of pregnant women in clinical research would be indicated by the actual increase in proportion of clinical trials that a) do not exclude pregnant women and b) those that are designed specifically for enrollment of pregnant women.
- The evaluation of impact on treatment of pregnant women would be indicated by an increased proportion of drug labels that include evidence-based recommendations for use in pregnancy and by case reports or surveys of practical experience in obstetrical practice. Labeling changes would include information specific to use during pregnancy including: pregnancy indications, dosing changes in pregnancy, pharmacokinetic information, and new safety information.
- The financial costs to industry – the costs of conducting the trials, related infrastructure and administration, delays in approvals, experience with litigation, etc., – and their offset by the financial impact of any implemented incentives. These will be more difficult to measure.

## **Benchmarking / Best Practices**

As the practice of including pregnant women in clinical studies will be new to the research community, benchmarking and sharing of best practices will be vital to the continuing improvement of clinical research practices involving pregnant women. Sharing lessons learned by experience would be facilitated by ongoing participation and monitoring by the proposed PhRMA committee on maternal health.

## **7. Limitations**

Rarely occurring adverse effects, including birth defects, may not be identifiable until a large number of people have taken the drug. Safety surveillance compliments clinical research data and needs to continue throughout the life-cycle of all products.

Concern has been raised that it may not be possible to enroll enough pregnant women to achieve statistical significance. Because pregnant women have been routinely excluded from clinical studies we do not know to what extent they might volunteer to participate. Pregnant women could only be invited to participate if they are in need of treatment, if the study would potentially provide therapeutic benefit, and if the potential benefits exceeded the potential risks. In this way, their treatment in a research study would be similar to their treatment in clinical practice - with the added benefit of improved informed consent, enhanced pregnancy monitoring, and the knowledge that she has contributed her experience to the accumulated medical knowledge base to assist other pregnant women. Currently, evidence from pregnant women treated in clinical practice is rarely captured at all. One small study found that 95% of pregnant women interviewed said that they would participate "if there is a chance that participation in a clinical trial would help their pregnancy and improve their baby's health."<sup>(21)</sup> Further research is needed to confirm or refute this finding.

## **8. Conclusion**

Women's health advocates, medical experts, and key informants within industry and related organizations believe that pregnant women and their fetuses are at a higher risk of adverse



medical consequences if they are not included in clinical trials than if they are included in clinical trials.(1,9,11-13) They believe that conducting trials on drug treatment for pregnant women, while ethically, legally, and operationally challenging, is morally required and will be advantageous to pregnant women and their fetuses, their health care providers and prescribers, and society in general. By issuing the draft guidance on the inclusion of pregnant women in clinical research, FDA is challenging industry to confront assumptions and past practices and address the obstacles that prevent effective, evidence-based treatment for pregnant women and the fetuses they carry.

**Note on the Author:**

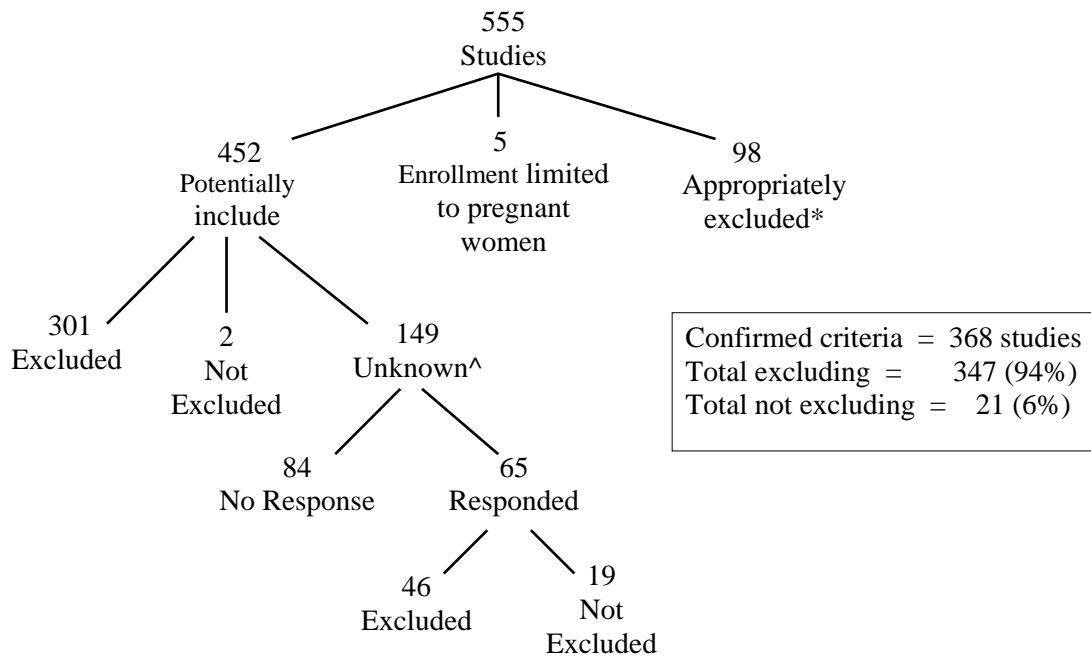
Kristine Shields MSN, DrPH is an OB/GYN Nurse Practitioner with a doctorate in Public Health Administration. She joined the industry in 1998 where she developed and managed a pharmaceutical company's Pregnancy Registry Program for 12 years. She is currently an Ethics Officer at the company.

# White Paper Addendum I

## Quantitative Study Findings

Results of a study designed to ascertain the proportion of clinical trials that excluded pregnant women by reviewing the inclusion and exclusion criteria of all U.S.-based, industry-sponsored Phase IV studies enrolling women of childbearing potential posted on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) between October 1, 2011 and January 31, 2012.<sup>f</sup>

### Number of studies available for review on ClinicalTrials.gov between 01Oct2012 and 31Jan2012 and their enrollment of pregnant women.



\* Pregnant women were excluded because the drug was in FDA Category D or X, or the age or topic (menopause, contraception, lactation) prohibited pregnancy.

^Study coordinators were contacted if enrollment criteria posted did not address pregnancy.

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<sup>f</sup> Shields K. Dissertation: The participation of pregnant women in clinical research: Implications for practice within the U.S. pharmaceutical industry; 2012. Chapel Hill, NC: University of North Carolina Gillings School of Public Health.

## **White Paper Addendum II**

### **Company Indemnification**

While many of the study participants were doubtful that indemnification was a real possibility, several of the pharmaceutical company and IRB participants recommended not dismissing the concept of company indemnification outright. They thought that the concept should be included when considering *all* the potential solutions to improving knowledge of pharmaceutical therapy for pregnant women.

Pharmaceutical industry concern about both the cost and the potential harm to a product and to a Company's reputation is a legitimate barrier to the implementation of efforts to increase the enrollment of pregnant women in clinical research. The following four points should be considered:

- **The President's Commission for the Study of Bioethical Issue's** recommendation of a national compensation system,(22) which states that "Because subjects harmed in the course of human research should not individually bear the costs of care required to treat harms resulting directly from that research, the federal government, through the Office of Science and Technology or the Department of Health and Human Services, should move expeditiously to study the issue of research-related injuries to determine if there is a need for a **national system of compensation or treatment for research-related injuries.**"
- One of the conclusions of the 2000 University of Texas Medical Branch conference held "to address the national problem of underrepresentation of pregnant women in clinical trials" was that "[t]here should be a **nationally supported mechanism to protect private sponsors and industry** from excessive or inordinate liability claims and to develop incentives to promote industry-supported research on this population."(23)
- The success of the **Vaccine Injury Compensation Program**, and
- The potential for **industry-sponsored group insurance.**

For FDA and PhRMA consideration: Consider an agency-industry-legal working group to explore the **feasibility of indemnification**. The adoption of the practice of designing and conducting studies for pregnant women may rest on the outcome of this question. Jury awards for children with birth defects and developmental disabilities – rightly or wrongly attributed to drug exposure – can be severe. Litigation costs can remove effective products from the market (e.g., Bendectin). Potential break-through medications are removed in early development due to this concern. Improvement in maternal health and positive pregnancy outcomes relies upon accurate knowledge of the safety and efficacy of treatment options during pregnancy. Systematic research is required to obtain this knowledge but litigation may prevent it.

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