Supplemental File

The Participation of Pregnant Women in Clinical Research:
Implications for Practice within the U.S. Pharmaceutical Industry

Pharmaceutical industry stakeholder perceptions of opportunities for, and barriers to, the inclusion of pregnant women in clinical trials

QUALITATIVE STUDY RESULTS

Results from Key Informant Interviews

Responses to Questions 1 through 10
**Question 1. Control**

Who has the most control over whether pregnant women are included in clinical trials – the pharmaceutical company (Sponsor), the Institutional Review Board (IRB), or FDA?

"[Y]ou need…the Sponsor, you need the IRB, you need the FDA, -- and you need the facility, too."

All respondents acknowledged that all three stakeholders have influence and share responsibility for the decision to include or exclude pregnant women from clinical trials.

"The Sponsor has to be willing to conduct the research, the FDA has to be willing to sanction it, and the IRB has to approve it. It's like a pyramid or a triangle. We all have to have buy-in."

"The Sponsors….write the protocols and provide the inclusion and exclusion criteria. IRB has absolute power to change it. FDA has absolute power to put a clinical hold on it." Any one of them could stop the study from moving forward. "I would say that any of the three probably have a veto in the sense that pregnant women are not going to be enrolled in a trial unless all three of those groups agree."

However, most also agreed that, although all three stakeholders have the ability to influence the final decision, ultimately it is the Sponsor who has the most control. Reasons cited by the participants for the pharmaceutical company's dominance included that the Sponsor:

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

Says one participant, "...an IRB can be comfortable or uncomfortable, the FDA can be comfortable or uncomfortable, but it seems that the people running the clinical studies, sponsoring the clinical trials in pharma, are the ones who will bear the immediate responsibility if something is perceived as going wrong -- that may or may not be related to the drug exposure."

Also, the interviewees felt that the consideration of the inclusion of pregnant women would only arise if the Sponsor suggested their inclusion. The FDA and the IRB would then respond to the proposal. They felt that, at this point in time, it would be unlikely for a Sponsor to exclude pregnant women and have FDA or the IRB recommend that they be included. One respondent said, "the FDA and the IRB can't force the company to include pregnant women in the clinical trials because ultimately it's a question of liability. So they're not the ones who are accepting the liability risk."

Not everyone agreed, however, and a few perceived the IRB as having the most control. A pharmaceutical company lawyer said, "[U]ltimately the IRB is the one that primarily has [the decision on] the inclusion of pregnant women; it is fundamentally an ethical issue that the IRB...has ownership of. But I think all three really share responsibility." An IRB employee
stated that "the company can write the protocol, they can present it to the FDA, but the last word of approval really comes from the IRB."

Another suggested the IRB and FDA together held the most power. "I think it's the IRB and the FDA [that] have...more control because even if the sponsor wanted to set up an arm or a sub-arm to look at pregnant women, there's an absolute need for FDA approval of that part of the protocol and then getting the IRB to approve it."

Overall, FDA was perceived to have the least influence on the decision to include pregnant women in clinical trials. Said one participant, "As far as the FDA, my impression is that it may not be common for them to comment but [they] would defer to the IRB since there is no regulatory prohibition. They would take a secondary role."

IRB review was noted to have some limitations. A company employee noted that IRBs only see one protocol at a time; they do not see the other protocols in development for the same product. They wouldn't know if a company was designing other studies that included pregnant women. Another noted that, "one of the issues we work on at PhRMA, which still has a way to go, is for multicenter trials to get greater acceptance of using a central IRB simply because of the variance of IRBs in terms of accepting a trial in a number of areas."

Of note is the identification of a fourth important stakeholder: the research institution. An IRB executive stated that, "the IRB can review and approve the study and ...feel it's perfectly safe and all the risks have been minimized, and there is terrific benefit, but .... if the
hospital's not okay with the conduct of the study, it will never happen."

She continued, "So you need all four points today – the Sponsor, you need the IRB, you need the FDA, and you need the facility, too."

Some participants volunteered their perceptions of how the stakeholders would respond to the issue. Of the three major stakeholders with input, one participant felt that IRBs "are the most resistant to allowing women who may become pregnant enroll into clinical studies, followed by regulatory agencies, followed shortly thereafter by Sponsors."

This pharma company employee continued, "the biggest contemporary challenge would be ethics review committees, IRBs. I think in part it's because their focus is rather narrow and they are diverse bodies. I don't think they're always necessarily in step with contemporary thinking in clinical trials. Oftentimes they're very individual patient-focused and often even lose sight of the wider patient population focus. I still think that they're your biggest problem or controlling factor."

An IRB executive confirmed their caution. "Once we see the word pregnancy, we step back and take a really close look at this. There's just so many things that could go wrong and you don't want to have not considered all of the risk factors."

A pharma physician thought the FDA would be inclined to approve the inclusion of pregnant women "if you could specify why you felt that the study you were doing was of benefit to the patient population that doesn't have that treatment option or you need more information or data for that patient population and there isn't a significant safety issue that you know about. I am of the opinion that the FDA would be fine with that study" She continued, "It's just been
“my experience that pharmaceutical companies, if you say pregnancy, everyone just sort of turns off, they switch off. It's like we don't really deal with that.”

**Key Findings for Question 1:**

The Second Wave Consortium workshop identified two key missing pieces of information for which they sought clarification. This question addressed one of them – what is the strength of industry's role in affecting the outcome of the debate on the inclusion of pregnant women in clinical trials? (The second was on litigation risk – see Question 4). Among the pharmaceutical industry researchers and lawyers, IRBs, PhRMA representatives, and FDA, the consensus was that the pharmaceutical industry has a dominant role in influencing the outcome of this debate.

**Key finding #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.

**Key finding #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.
Key finding #1c: 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).

Key finding #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.

Key finding #1e: All of these stakeholders were perceived to be resistant to the idea of including pregnant women in clinical trials.
Question 2. Awareness

Are you aware of the FDA Guidance? Have you heard of the Second Wave advocacy group?

"Who's really advocated for clinical trials in pregnant women?"

Awareness of the Second Wave Consortium

Most participants had never heard of the Second Wave Consortium. Of the 2 participants who had, one was at FDA and one worked at a Biotech company. Both said they had heard mention of the group by a speaker at a conference. The FDA interviewee thought that the Second Wave Consortium was doing important work in getting the issue into the public domain. "Because of the seachange that we have to have here, and because there are so many stakeholders in this conversation, this is how we're going to get started."

Other participants concurred that there is a lack of awareness of the issue that may hamper efforts to change. One said, "[T]here's just been no interest in looking at this. There's not been anyone to advocate for it, right? So, it's like the difficulty with pediatrics. Over the longest time there was just not really sufficient advocacy for the position from the right stakeholders, until there was some financial incentives. This is even starker- who's really advocated for clinical trials in pregnant women? Until you told me about the Second Wave, I hadn't heard about anything."

Awareness of FDA Draft Guidance
Similarly, most participants were not aware of the draft FDA guidance that is currently in review at the agency. Obviously, the FDA staffer was aware, but the PhRMA representative was not aware. A couple of participants (one in IRB and one in biotech) had learned of the draft guidance because its title was included on the FDA guidance to-do list published in "The Pink Sheet" in January 2011. Two industry employees (one biotech and one pharma) questioned whether the current draft guidance is a new iteration of a previous draft they had heard about "some years ago."

The FDA representative confirmed that the draft guidance is "working its way through the system of review and clearance," which, she stated, can "move ponderously slowly." She feels, based on conversations in the public arena, that "there is a growing sense of comfort in the idea that one can do these studies, given the number of studies that...have been done in antivirals and HIV, and to some extent, the onset of concern around medical countermeasures." Regarding the latter issue she said, "You see the light bulbs go on when you talk about the ampicillin/anthrax issue. That's been a hallmark set of studies to really wake people up... Pregnant women may not be just like women of the same age who are not pregnant when it comes to medicines, and how are we going to deal with it?"

The ampicillin/anthrax issue, previously discussed in Chapter 1, refers to the 2002 recommendation by the American College of Obstetricians and Gynecologists of the use of amoxicillin to treat pregnant women who were potentially exposed to anthrax. The dosage and frequency regimen was found in subsequent study several years later to be ineffective in the treatment of pregnant women. The implications of this finding highlight the dangers of
generalizing data from non-pregnant subjects to pregnant women and the need for research on the target population.

**Key Findings for Question #2:**

Lack of awareness of the issue, which was seen as a prerequisite to advocacy, was consistently cited as a barrier to change. Most of the participants themselves were not aware that the issue is being debated in some quarters, nor were they aware that FDA has a guidance document in draft. Lack of awareness on the part of the general public was also identified as a critical issue, particularly because, as one participant stated, a "seachange" in thinking will be required to address it. 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.

Three opportunities were identified that could facilitate both awareness of the issue and its potential resolution:

1. Public and government interest in bioterrorism
   a. The "anthrax issue" was cited as an ideal illustration of the issue
2. Prior success in conducting clinical trials in HIV positive pregnant women
3. The success of the effort to include pediatric patients in the drug development process.

**Key finding #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.

**Key finding #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 felt to be important in this regard.

**Key finding #2c:** There is opportunity for change utilizing the government's and public's current interest in protection against bioterrorism.

**Key Finding #2d:** There is opportunity for change utilizing the work that has been done with pregnant women in clinical trials for HIV treatment and the prevention of vertical transmission to their fetuses.

**Key Finding #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.
Question 3. Policy and Practice

Does your organization have a policy about whether or not to include pregnant women in clinical studies? What are the current practices there?

"The practice is to exclude pregnant women. It's fairly entrenched."

The following quotes, from the pharma and biotech companies and lawyers in those companies, describe the status quo:

- I can't name one company that has done clinical trials with pregnant women.
- Current practice is to exclude women who are known to be pregnant.
- The practice is to exclude pregnant women. It's fairly entrenched.
- I know that it is, in fact, our practice to exclude pregnant women except in therapies that are designed to assist pregnancy.
- All our trials exclude pregnant women.
- I'm not aware of an actual policy saying that they shouldn't be in but they just never are.
- I think in this day and age they'd be apprehensive about putting it in writing but I think today it's a widespread assumption and convention that you just don't do that.
- I am not aware of any studies by any Sponsor that would include pregnant women.

Yet, there were a couple of pharma company employees that had experience with clinical studies that included pregnant women. One woman stated that companies "don't want something bad to happen to a pregnant woman or her fetus or her newborn relative to their drug. So they are cautious more than anything." Her experience involved products to treat
HIV and to prevent vertical transmission to a fetus. Prior to the initiation of the company's studies, information on their drug's use in pregnant women was available from pregnancy registries and from NIH trials. With that safety information on hand, she was able to design additional studies for pregnant women. She stated that, "the problem with industry is, the people who are going to make the decisions, are they knowledgeable enough about the drugs, the safety profile of the drug, of the data, and the therapeutic area in need? If they understand all of those things, I think the discussions go a little bit faster and a little bit easier. But if they don't understand, if they don't have that knowledge base, then you have a lot of hurdles to overcome in industry."

Another company employee described the oversight boards and safety monitoring boards that the clinical trial protocols go through prior to study initiation. A (theoretical) study for pregnant women would have such oversight as well, he said. Even now, if a woman becomes pregnant on a trial and her PI feels that it would be in her best interest to continue on the study drug, the PI can request a protocol exclusion to keep her enrolled on a compassionate use basis. "Generally," he said, "the patient is immediately withdrawn but there is the opportunity to challenge that."

There is no PhRMA Organization statement on the inclusion of pregnant women in clinical trials. The organization person I spoke with stated that this issue has never come up in conversations with the FDA Office of New Drugs. And, he added, "quite frankly, most of what PhRMA does tends to be reactive rather than proactive. So that when FDA will issue a draft guidance for comment, PhRMA would then convene or develop a group....to prepare
comments for it." He was unaware of the guidance in review at the agency on this topic before we spoke.

The IRBs, however, had more detailed responses to this question. Each IRB interviewee stated that they do have a policy on pregnant women in clinical trials – it is their policy on "vulnerable populations." One said, the policy "talks about subpart B of subpart 45, it talks about various concerns or considerations when including pregnant women. Generally, what it outlines is that pregnant women may be included in a clinical trial – again, if it's in compliance with the regulations, and also if the board thinks that it's essentially ethically acceptable."

One IRB executive stated that, "We do have a policy, because you can't leave them out of everything. Because if you leave them out of everything, you'll never learn anything, and they have the right to be studied just like anybody else does. You need information on them like for everybody else. You can't exclude them because that would be unfair. But you just have to be very careful when you do include them." However, one of her IRB colleagues considers minimization of risk to come before the equitable selection of subjects, stating that, "even before the Belmont principles really, beneficence and nonmaleficence rise to the top of the list and autonomy is lower down."

The IRB members I interviewed also talked about the draft FDA guidance. One said, "I think that once they have laid out what they would consider clear-cut guidelines for the enrollment of pregnant women in research, I think that more IRBs would be more willing to take a look."
The FDA guidance will be helpful." Another stated that, "I think that as soon as there's guidance put out there, and one IRB reads it and feels that they can actually provide proper oversight, that women will be able to be enrolled in clinical trials even though they're pregnant." Another one stated that, while their policy is somewhat general at this time, "it will be more elaborate if the guidance came out."

The FDA interviewee, a former pharma company employee, stated that, "Unless the company is dealing with some very specific disease area, I don't believe companies will go there." "A mark of success to me," she added, "will be the company that has in its research plan for a chronic drug for depression, a plan to enroll pregnant women post-marketing. But at this point it's going to be restricted to those specialty areas where it is clear that the studies haven't been done in the past and they'll be expected to do them. Like some of the tropical diseases, the developing world concerns, malaria comes to mind."

**Key Findings for Question #3:**

The consensus was that current practice is consistent: pregnant women are almost universally excluded from enrollment in clinical trials. When women become pregnant during a trial, current practice is to immediately withdraw her from the study. There is an option for the PI to request continued inclusion on a case-by-case basis, as is true in general for study participants, but it was suggested that utilization of this option is rare.

Some industry respondents indicated that although the woman is disenrolled, the study coordinators maintain contact with her and collect information on the outcome of the
pregnancy. But others stated that not all pharmaceutical companies do this kind of follow-up as it is not required by regulation.

One of the participants had practical experience in conducting studies in pregnant women. She found two factors very helpful in that endeavor - safety data on the use of the product in pregnancy that may be available from government-sponsored studies and pregnancy registries, and decision-makers within the company who were familiar with the interpretation of drug safety data and the therapeutic needs of pregnant women.

Researchers and IRB members discussed the ethical principles involved when considering the enrollment of pregnant women. Non-maleficence (do no harm) was cited as the main cautionary principle but justice (the inclusion of all groups who may benefit from the treatment) and autonomy (the right to decide for oneself) were mentioned. One IRB member stated that not all principles were weighted equally. He felt that non-maleficence transcended autonomy – a perception apparently shared with others as reflected by the status quo. The FDA participant thought that initial studies that include pregnant women will likely be conducted in specifically identified therapeutic areas – perhaps making it easier to justify the risk by choosing well-documented and widely accepted areas of need. Both IRB and PhRMA participants agreed that the FDA guidance document on the subject will improve consideration of the topic and strengthen their policies.

**Key Findings for Question #3:**

Key finding #3a: Most companies exclude pregnant women from their studies.
Key finding #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 the FDA guidance on this topic.

Key finding #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.

Key finding #3d: FDA feels that studies should be done for certain products where the need is well established.
Question #4. Reasons for Exclusion

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."

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 to running 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 not the historically acceptable way to do business.

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<th>Most Cited</th>
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Areas of confusion

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 was further explored, and is therefore addressed, in the following section.

A. Do no harm: beneficience and non-maleficence
"the risk to the fetus... is a historically insurmountable hurdle."

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. I think that's the primary reason. I think that would be far and away the most important."

From another company lawyer – "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. So, exclusion is because we cannot strongly support that the benefit to the mother outweighs the risk to the fetus yet.

"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 so 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."

"Do you even know how to dose it? I think [the anthrax experience] is a very cautionary example. You better check on your dosing if you're doing [trials in pregnant women]."

B. Scientific validity: Data interpretation

"Pregnancy is just an outlier."

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 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."

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.
- Pregnant women may affect drugs differently than non-pregnant women.

"Women's bodies are different during pregnancy and so you're not sure how that may skew the results of the drug or device being used on the woman." "How [is] the [pregnant] woman's body going to affect how the drug is going to react" or be metabolized? 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.

Even 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.

"You're not likely to get enough pregnant women to really draw conclusions. So...if you
allowed pregnant women to stay in a study, you will have really small number that really
won't allow you to draw statistical conclusions because your sample size is so low."

"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."

C. Evaluating teratogenicity:

"Thalidomide has really scared a lot of companies"

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 and those attributed to drug exposures are very low (about 2% of the 2 to 4%).

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 participants is that the birth defects 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 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 complete 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."

"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."

D. Regulatory rationales:

"It's just like a black hole."

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. One respondent 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. An FDA employee reasoned 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 participant, 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 is 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."
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." "Industry constantly thinks about the risk to the drug."

The conduct of clinical trials in populations that are peripheral to the primary target population is a secondary concern. On this topic, participants stated that, "They're not going to go there until they know this drug is going to make money for them," "[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."

In the context of business, several participants named adverse notoriety for the company as a reason to avoid testing the drug in pregnant women. "If 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 to recover from.

"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..."

F. The risks of research and pregnancy

"It's risky research."

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." 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..."

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."

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. An IRB respondent said, "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."

Another IRB representatives had a similar view, "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." The status of the fetus as an entity whose needs, in some regards, it is suggested, should be considered as independent from the pregnant woman were raised in the responses to this study and could be considered to be a barrier to the inclusion of pregnant women in clinical trials.

F. Limit testing to drugs indicated for use by pregnant women
"[T]here's actually a risk of non-treatment to the fetus as well."

"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)."

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 marketplace, are there other 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. 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.

G. Lack of advocacy

"There's not been anyone to advocate for it."

Like the participant quoted in question one who said, "there's just been no interest in looking at this. There's not been anyone to advocate for it," others concurred. "It's not very high up in the consciousness of most people conducting clinical studies." 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." And yet, there are suggestions, like the draft FDA guidance and the Second Wave Consortium, that advocacy has begun. From the FDA interviewee - "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 Question #4:**

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. In order to fully evaluate the issue and to potentially devise
means to alter the status quo, we need a better understanding of the potential barriers perceived by this powerful stakeholder.

**Key finding #4a:** The fear of causing harm to a fetus is the most important concern limiting the inclusion of pregnant women in clinical trials.

**Key finding #4b:** The fear of litigation is one of the major concerns that is limiting the inclusion of pregnant women in clinical trials.

**Key finding #4c:** 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 #4d:** 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 #4e:** National and international regulations regarding the inclusion of pregnant women in clinical studies are not well understood.

**Key finding #4f:** Studying drugs in pregnant women would provide valuable information for the label, which would improve the treatment of pregnant women.

**Key finding #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.
Key finding #4h: 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 #4i: Industry perceives little motivation or advocacy for the study of its products in pregnant women.
Question #4.a. Litigation

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."

This question was asked to the participants who raised the issue of litigation. 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.

Said one physician, "...when you talk to the OB people, one of the reasons why the liability is so high is that we get blamed for all the abnormalities that could occur, ....I hear that there are a lot of malpractice suits concerning congenital anomalies..."

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

One pharma company employee said, "people are suing already when we are excluding them." When asked to explain, he said that his company has litigation pending 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."¹

The issue of informed consent was raised by several participants such as this one 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."

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."

An IRB executive stated, "I can count on one hand the amount of calls that come to me where someone was actually damaged or injured in a clinical trial and they needed an attorney. That's over 15 years."

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 Question 4a:**

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 #4a1: 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 #4a2: There is also 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.

Key Finding #4a3: 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 #4a4: 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 #4a5: The risk of liability for injuries that occur during research in general is low.
Key Finding #4a6: 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.

**Question 4.b.** 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."

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 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 two: "in the post-marketing environment the prescribing physician has the decision-making responsibility," and, 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." Another of the three 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 last of the three 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 4A. Factors that increase the risk of litigation in the clinical trial and post-
marketing environments

<table>
<thead>
<tr>
<th>Factors that increase the risk in the post-marketing environment</th>
<th>Factors that increase the risk in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>No informed consent</td>
<td>Little knowledge about the safety of the drug being studied</td>
</tr>
<tr>
<td>Lack of adequate testing / due diligence in clinical trials prior to marketing</td>
<td>No regulatory statement about safety (like the drug label)</td>
</tr>
<tr>
<td>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.</td>
<td>No learned intermediary prescribing the product</td>
</tr>
<tr>
<td></td>
<td>Current standard of care is exclusion – why were they testing pregnant women?</td>
</tr>
</tbody>
</table>

Table 4B. Factors that decrease the risk of litigation in the clinical trial and post-
marketing environments

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

Most of the interviewees thought that the risk of litigation was higher in the post-marketing environment for the reasons shown in Table 4A and 4B. 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, the 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. Versus in the clinical trial setting, everyone is aware, everyone knows it's supposed to be experimental. I really think there'll be more chance for litigation in the post-marketing setting."

"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 trial, 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, they are real world patients, they don't 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."

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."

From a lawyer: "Historically,…it's hard for a plaintiff to succeed if there was informed consent."

In spite of this, pharma 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?'" One 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, "the mood is moving strongly in the direction that any abnormality of the child is potentially suspect as a result of poor care by the obstetrician/gynecologist or the result of material that they were exposed to. 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.
Another 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."

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 spector of endless litigation."

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, "Well, 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 Question 4b:**

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 had it been tested in a clinical trial. A higher number of birth defects in the post-marketing environment might result in a higher risk for litigation.

A few of the respondents considered the risk to be higher in clinical trials because there is less known about the compound being tested. But most presumed it would be higher in an untested drug post-approval. The discussion was speculative, however, because we lack actual experience with the inclusion of pregnant women in clinical trials.

**Key Finding #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.

**Key Finding #4b2:** Fear of litigation may be deterring pharmaceutical companies from testing drugs in pregnant women in clinical trials.
Key Finding #4b3: Fear of litigation about birth defects may be deterring the development of potential pharmaceutical interventions that address unmet medical needs of the population.

Key Finding #4b4: There is a fear that evaluating the safety of a drug in pregnant women may increase a company's risk for litigation.

Key Finding #4b5: The risk of litigation is considered to be higher in the post-marketing environment than in the clinical trial setting.
**Question 5. Inclusion**

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?

"You're flying blind when pregnant women get sick"

When I posed this question to the FDA participant she responded, "You mean aside from the fact that it's the right thing to do?"

<table>
<thead>
<tr>
<th>Reasons to include pregnant women in clinical research</th>
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</thead>
<tbody>
<tr>
<td>It's the right thing to do</td>
</tr>
<tr>
<td>There is medical need</td>
</tr>
<tr>
<td>To assist health care providers</td>
</tr>
<tr>
<td>To fully evaluate the product's safety profile</td>
</tr>
<tr>
<td>To improve insurance coverage</td>
</tr>
<tr>
<td>To emulate best practices in other special populations like the elderly and pediatrics</td>
</tr>
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</table>

**Medical need**

The reason most often cited for the need to include pregnant women in clinical trials was to provide treatment for pregnant women who have medically compromised pregnancies.

"I think we have an unmet medical need which is, we don't know enough about these drugs to feel comfortable using them in pregnant women and therefore women who really need therapy for whatever conditions they have that is concurrent with their pregnancy, you have no information. So you might have women either taking a drug that they don't know enough about, or not taking a drug that they do need, and either way, we have no information to guide care. So guidance of care is a very important reason."
"There are about 4 million births in this country each year, so there are a lot of pregnant women out there, and a lot of women in their childbearing age that might get pregnant. And many of these women have chronic diseases that need treatment throughout pregnancy for serious diseases during pregnancy."

"How are we going to move forward? How are we going to be able to help those who need it if we don't conduct trials? The whole reason for research goes back to - it's the same question - we need the information."

"If we were studying a drug for a condition that had a high rate in women who might be pregnant, for example, diabetes, or a large number of people at risk for a condition where you might actually be treated before you became pregnant, you need to know what would happen. Should you stop the drug or can you continue it? The same kind of thing with HIV. You might be treated before you even get pregnant. You have to know can you continue it? So for anything that has a reasonable prevalence rate in women who are likely to get pregnant, it probably is worth studying - but maybe not before you get the original approval for the product - that's a different question. I don't think it's a box check, where every drug should be tested. It should be for a drug where the condition might reasonably occur in pregnant women."

"So if we consider that the segment of the pregnant population is an important population, and we know that women who get pregnant sometimes need to use medications, either
because they have a current condition or because they develop a condition during pregnancy, and they need the medication, we need to know of the safety of the medications. We need to know. Because those women, when the drug goes to the market, those women will need a medication and use the medication, and if we don't have information then we are putting that population at an even higher risk."

If the benefit exceeds the risk

"Sometimes we do know from doing animal models that the drug is safe... We know from phase 1 and phase 2 studies that the drug does have benefits, it's an effective drug. We have a pretty clear idea that it's safe and effective. And in the context of the higher benefits to the mother than the risks to the fetus, then in that context, there's no real reason to exclude these women."

Company reputation

"I think also the customers who use the product, if they know that the drug company is really diligent about monitoring the safety profile of the product in pregnancy, then I would personally be more likely to take that company's drug over a company that didn't do it. Because I would feel that the company that conscientiously really tries to evaluate it are the kind of people I'd like to take their drug and not companies who are not interested in evaluating the drug. The ethical things are...good PR for the companies and good [for the] reputation of the company."
Information for prescribing health care providers.

"If you're drug has a possibility of being used in pregnancy, you would want to have at least some body of data in the company database so that...you could advise physicians and clinicians when they are asking questions about whether it's safe to give that...drug to a pregnant woman that is a patient of theirs."

"I really think we've got to the stage whereby evidence is so much better than - I always go back to the evidence - it's so much better than guessing."

"Good data...will reduce the risk for providers. We have to remember that they assume a certain amount of risk with dispensing or prescribing a drug that might not have a lot of information."

To fully describe the safety profile

"The one area that I think that companies should include pregnant women in clinical trials is in vaccines because I think it's important. Like with the flu vaccine, a lot of pregnant women get the flu vaccine to protect their baby and also to protect themselves but nobody ever does studies in pregnant women. I don't think they do studies in pregnant women with vaccines, I haven't seen any. Pregnant women were at huge risk, they were the ones who were dying with the swine flu epidemic. So I basically think that if you don't include pregnant women in your patient population and they are a population who is likely to receive the product, the
vaccine, the drug, whatever, you have not adequately described the safety profile of your product."

**To develop medications to treat the population**

"I can come up with multiple reasons but the big one is so you can develop drugs that are actually known to be efficacious to use in pregnant women or understand how they may affect the fetus so I think it all just sort of relates to trying to derive a benefit for these pregnant women. I think that reason is, in and of itself, why we conduct research in general. We do research to further science that will hopefully benefit various populations to treat diseases and conditions and that's the whole reason why there is research and why we are developing new medicines."

**Inform labeling**

[The information] "can help you to work with the FDA or some regulatory body as to where to start in terms of how to categorize the drug in terms of FDA pregnancy category."

"And if we have no information as to such simple things as pharmacokinetics in that population, are we providing the best prescribing information for use of the drug in pregnancy? Whether it's formally approved for use in pregnancy or not, but just knowing that it could be used in pregnancy."
Improve insurance coverage

"One other reason may be to inform insurance companies because sometimes insurance companies have an influence on whether they will pay for a drug or not. Maybe this information [will] inform them so that they didn't disqualify the drug or tell a woman that she had to pay out-of-pocket because they wouldn't want to be involved in any potential liability or risk."

Competitive Advantage

A couple of participants rather reluctantly raised the idea of competitive advantage but did not place it high on their lists of reasons to do the studies.

"Well, I don't know if I really want to raise it, but it could be a competitive advantage... over another product, if you....see that you're effective in an area and have a better safety profile over a competitive product. I don't like to use safety for competitive advantage so that I'm kind of reluctant to make much of a case of that. FDA is very cautious about using safety as competitive advantage [too]."

Similar to other special populations like pediatrics and the elderly

From a company physician - "I don't think we should see pregnant women as something different. Pregnant women should just be seen as part of the patient population, as elderly are seen that way."
From a company lawyer – "I think it's maybe a similar approach to the way people thought about pediatric trials a while ago, which is that we don't want to risk harm to a child so were not going to use study drugs in them. And then it became apparent that, nevertheless, children needed treatment for conditions and so many physicians were prescribing products without an adequate understanding of the risks and benefits. And it became apparent that, from a society point of view, [we need] to actually conduct the trials and figure out what products worked and what didn't. So I think it's the same thing there, if you get past the ethical hurdle, you do have this issue of knowing that pregnant women, for some conditions, need to be treated. And that if you know that women need treatment of some sort, there's an argument that you may as well figure out what treatments are safe and appropriate. I think that's only one reason - but I don't know what the other three or four would be. Maybe I'm too stuck on the ethics piece."

**Key Findings to Question 5:**

**Key Finding #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.

**Key Finding #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.
**Key Finding #5c**: 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.
Question #6. How to enroll pregnant women

If pregnant women were to be enrolled, how do you think we should do that?

"[W]e have a lot of great medical minds and...we need to put them to work."

Most participants agreed that if there is "preclinical information that makes one think that the risk is small relatively minor to the fetus" - or - there is "clinical evidence that the drug has benefits that outweigh the potential risks" then pregnant women can and should be included in drug development studies.

The interviewees suggested that the following information should be available, and should be taken advantage of, when planning studies in pregnancy: data from modeling, pre-clinical data on use in pregnancy, metabolism in the non-pregnant state (anticipating it would be modified by pregnancy), information on other drugs in same class or with a similar structure, outcomes from inadvertent exposures in clinical trials, biomarkers to evaluate fetal or pregnancy impact, and all information available from pregnancy registries, surveillance programs, or other studies that have been done (e.g., NIH).

More than one suggested that pre-clinical evaluation is an area where exciting new methodologies are currently being developed, like biomarker assays, molecularly targeted agents, genomics.

• "I think we are still in our infancy in knowing many of these things."
• "Phase 0….that's when you use microscopic amounts for which you have really good analytical techniques for the amounts….If you have strong analytic methods, you don't need much product to show the pharmacokinetics."

• "I think you've got to go into the world of looking at assessments that we don't normally do in the standard drug development paradigm. I'm thinking particularly about modeling, Pd and PK kinds of things and making assessments that may be are in or outside the realm of a clinical trial and we have to figure out how the data that comes from those types of studies can be integrated into what we know about the drug to make risk assessments. I think the advancement of that science is going to be critical for the widespread acceptance of trials in pregnant women. I'm hoping the people who work in this field begin to advocate for it a little bit more. And it's also going to take some of the clinical trial specialists to think out-of-the-box a bit, for the larger companies to say, 'hey, we can advocate for this kind of data showing us what we need to know and we don't have to put the drug in a person.' Again, I think that's actually where some of this anthrax work is going to take us outside of the issue of pregnancy. Some of the things we just don't want to test but we will have to figure out how to treat."

The FDA participant also suggested "more emphasis...on the non-clinical reproductive data. We need to go back and look carefully at the embryo/fetal development studies and see if we are getting all the information we need out of those studies to support trials in pregnant women. If we can get that process into the drug development planning that would be just a huge milestone because you could then plan your preclinical work and non-clinical work to
accommodate all of the populations that you anticipate that the drug will be used in. I think what those studies are lacking is a good characterization of pk compared against the non-pregnant animal so that you get a sense of what pregnancy does – understanding completely that pregnant rat physiology is probably different from a human but still the comparison holds. And I think there's a lot more work we can do in the early clinical trials to characterize the changes in physiology that occur with a drug that would help us set up for a trial like this. It may not even be added data collection, it may just be a difference in how we do the analysis [on the data that we have already collected]."

She continued, "If there's a lesson to be learned from pediatrics, I think it's this one: it's that you need to embed the message that planning early is the success here. That when you are in that space around proof-of-concept, somebody ought to be sitting down and saying, 'is this drug anticipated to be used during pregnancy?' And if so, when are we going to make plans to do the appropriate testing? And if it's going to be Phase IV, do we have all of the preliminary work done? ...[D]o we need to adjust our non-clinical work? Do we need to have added emphasis on the pk in women? And just slot it into the normal development program as it goes so you have all of that information ready when it's time to decide if you're actually going to execute on that study. That's the kind of line of questioning that I think major companies are finally now doing for pediatrics because they've got it figured out that they... have to pay attention to their toxicology so they don't get caught short and have to go back and retread work when it's time to do those studies."

Participants had a number of suggestions about how to conduct clinical trials in pregnant women. Most agreed that the conduct of the study should wait until safety and efficacy data
had been gathered in clinical trials, therefore, studies in pregnant women should not commence until late Phase III, or even Phase IV.

- "...it would be inappropriate for any company to want to include [pregnant] women in these trials until they have a really good handle on the safety profile of that drug."
- "[I'd be]...reluctant to give [a new] drug to a pregnant woman not knowing anything about the efficacy and subjecting her to the potential of having a congenital anomaly. I'd...want to take a look at the animal tocixology data, knowing full well that it's difficult to translate animal data to humans... If I thought the disease was serious in a pregnant woman and the drug really had good efficacy then I would very much consider enrolling women but it would probably be after I have efficacy data so that I know it works. I would probably do it near the end of the clinical trial development."
- "The studies in pregnant women are crucial questions. [The question] is at what point in drug development do you do that? I personally would prefer doing them after I had some efficacy data showing that the drug really does work and the woman has a good chance of benefitting from it."

Similarly, most stated that trials in pregnant women should not commence until the women are in their second, or more likely their third trimester, in order to decrease the risk of inducing a congenital anomaly in the fetus.

Another participant recommended "doing like they did in pediatrics, I would have something in every New Drug Application...you would put together a Pregnancy Investigational Plan. Now they could have upfront guidelines for when they would grant waivers, but there might
have to be potential waivers, if it's a drug for only people over 80 are under eight or something of that nature. But have them put in the plan and that if the plan is accepted then it would proceed with a lot of input and joint work together with FDA and if possible with other experts that there would be some reward for completing the studies and if it's good accurate labeling data it should be there."

He also suggested "putting something more ominous in the labeling than 'studies than in pregnant women have not been conducted.' They might put something in there that says 'these studies weren't conducted and they should have been conducted.' So there is a bit of the stick - the company has been told you have to do this and there's a penalty for not doing it, but there's a reward for doing it, you're not out there all alone, we're all in this together and we'll use the best of our collaborative abilities to do it."

We would not be starting from scratch. The participants were aware that information on the development and conduct of trials in pregnant women is available from published papers and experienced clinicians e.g., HIV trials, NIH Women's Health Studies. "In the HIV field, you could say that we have done a lot of the pioneering work to proactively study the drugs without being instructed or advised by the regulatory body. Once we recognized that we could impact the spread of sexually transmitted disease and save lives, we have actually been very proactive and our thinking has been prospective in trying to get as much data as possible in order to safely administer the drugs to pregnant women."
One such experienced physician described making clinical trial visits the patient's routine OB visits as much as possible to decrease the burden on the participant. One of her trials covered all lab work, ultrasounds, medications, evaluation of the baby at birth and in follow-up visits, so that the patient, her health care provider, the insurer, and the institution did not bear the costs. This was in addition to compensating the women for their time.

Others felt that data should come from wherever it can be found and should be ongoing for the lifetime of the product. "Large observational databases, prospective registries, other registry inquiries, etc. All those things should be taken together. Planning a clinical trial might be with the upfront expectation that the clinical trial is just part of an overall program and the clinical trial would be followed by long-term follow-up of the fetus or ascertainment of exposure by other means." Another added that "the cumulative experience including long-term follow-up with the agent of interest should be applied iteratively to each new study or enrolling patient" in order to provide the patient and the health care providers with all the information available to maximize informed consent.

**Key Findings for Question 6:**

**Key Finding #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.
Key Finding #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.

Key Finding #6c: There are manageable ways to design studies that minimize risk to pregnant women, their pregnancies, and their fetuses.

Key Finding #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.
**Question 7. Safeguards**

If pregnant women were enrolled, what steps could be taken to safeguard the fetuses and the pregnant women who consent to participate?

"[I]t is difficult for industry" to make these "very difficult ethical considerations when it's a subject of so much external criticism."

In many, but not all cases, participants answered this question in previous discussions and so were not asked it again during the interview process. However, some additional thoughts were recorded on this subject.

Steps that were recommended to be taken before initiating a clinical trial included an evaluation of the alternative treatments available to make sure they would not be more appropriate, a thorough review of the animal toxicology data, understanding the pharmacokinetics and pharmacodynamics of the drug, does it cross the placenta, what percent is protein bound, and looking at other products in the same drug class or with a similar molecular structure.

During the course of the study additional fetal monitoring, more frequent study visits, and having specialists in maternal-fetal medicine involved in the design and the conduct of the study were all mentioned.

One industry physician recommended that we keep evaluating the data on an ongoing basis being alert to any signals that might be meaningful. He said, "You have to keep looking at
this - whether it's results of prior clinical studies, results of observational data, as you keep
looking at this and refining over and over again, if you're planning a new study or if you're
enrolling the next patient into the next study. Each pregnant patient entering the study should
be able to benefit from the knowledge gained from every patient that has gone before her in
this type of the setting."

An industry lawyer recommended an independent oversight group he described as "sort of a
super IRB that can be maybe an extra powerful data safety monitoring board….that would be
the one to make these difficult ethical decisions." He said he didn't think industry would
engage in this kind of research without one. "[I]t is difficult for industry" to make these "very
difficult ethical considerations when it's a subject of so much external criticism."

**Key Findings for Question 7:**

Suggestions about how to minimize risk were offered for consideration. Many participants
felt that there are subject matter experts within and outside of industry who could be
consulted about how to design a trial for pregnant women that would safeguard the woman,
the pregnancy, and the fetus.

**Key Finding #7a:** Data collection and analysis should be applied in an iterative fashion so
that each pregnant patient entering a study should be benefit from the knowledge gained from
every patient that has gone before her.
Key Finding #7b: A pregnancy-specific independent data safety monitoring board should provide oversight and decision-making functions.
**Question #8. What would it take?**

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."

"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."

"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 this into the next step for research in the 21st century. I think we still very far from it."

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. [. . .] [T]he 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." Another participant concurred, "The experience with studies in children suggests that a regulation would be necessary." 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."

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."

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."
"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."

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 one respondent, "you get additional clarity that is quick and adaptable, easier. Regs are too vague, guidance can be more detailed." Another participant observed that guidance recommendations "can be achieved more easily and harmonized more easily" across institutions, states, and even across countries.

**Question No. 8.b. 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."

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.

From a Company physician, "I think there are instances were 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."

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. He stated that, "[t]here 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 issue². .... 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." 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.]³ 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.

Another participant responded, "Well, so a guidance document is interesting but probably would not be sufficient to overcome the other concerns that companies have. Carrots, like a

² http://bioethics.gov/cms/node/306. The "Guatemala issue" refers to a recently uncovered study conducted by the US Public Health Service in that country in 1946 to 1948 involving the intentional exposure of subjects to sexually transmitted diseases without their consent.
³ http://en.wikipedia.org/wiki/National_Childhood_Vaccine_Injury_Act
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."

**Question 8.C.** Would patent extensions, like those implemented for pediatric trials, be a viable enticement?

"Be careful what you wish for."

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, because if you're going to take the risk of doing it, the patent extension may make it worth your while." "Patent extensions have worked for pediatric exclusivity; it could possibly work in this particular case." "A Company is taking extra risks that have monetary value."

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."

However, others expressed dissatisfaction with their patent extension experience in the
pediatric sector. Said one Company participant, "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."

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 one participant. A pharma
lawyer agreed, stating that, "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 PhRMA lawyer 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."

**Question No. 8.d.** 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."

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 Q8a. Observations, suggestions, and potential solutions**

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<tr>
<th>Observations and Recommendations</th>
<th>Solutions</th>
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<td><strong>On the Business</strong></td>
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<td>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.</td>
<td>Establish commitment at the top</td>
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<td>My hope is that the guidance would at least drive the companies back to reviewing their current feelings on this.</td>
<td>Respond to FDA guidance</td>
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<td>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.</td>
<td>Make routine part of drug development</td>
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<td>[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.</td>
<td>Public Relations Opportunity</td>
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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.

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.

In pediatrics, there's a market; with pregnant women,…not very much. So from a commercial perspective, it is completely unappealing for the Company.

**On Litigation**

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.

I think if …there was some liability for not treating the woman when you could save her life or spare her from increased morbidity, I think that might persuade them as well.

**On FDA**

…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.

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.

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.

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.

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
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. 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…

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<tr>
<th>On Advocacy</th>
<th>Provide a financial incentive to Sponsors of studies</th>
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<td>I think it needs to be on the agenda of Pharma 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.</td>
<td>Involve professional industry and medical groups</td>
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<td>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, that's why I mentioned the professional organizations, as well as Pharma and Bio. …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 agenda for 2017 - in 2015 for the 2017 PDUFA.</td>
<td>Sustained advocacy by central advocacy group; develop position; involve stakeholders</td>
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<td>For policy advocacy, use anecdotes. They work. The anthrax example is a good one.</td>
<td>Use anecdotes</td>
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<td>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.</td>
<td>Involve stakeholders: academics, clinicians, pregnant women; professional organizations</td>
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<td>[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 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.</td>
<td>Bring stakeholders together in public forums</td>
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<td>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.</td>
<td>Remove the vulnerable population label from pregnant women</td>
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4 [http://en.wikipedia.org/wiki/Prescription_Drug_User_Fee_Act](http://en.wikipedia.org/wiki/Prescription_Drug_User_Fee_Act). The Prescription Drug User Fee Act (PDUFA), passed in 1992, permits FDA to collect fees from drug manufacturers to fund the drug approval process. Consumers, industry, and FDA, had complained that drug approvals were taking too long. FDA had been requesting additional funding from Congress to manage the backlog and streamline the process. The law succeeded when FDA and industry agreed on setting target completion times for drug applications and ensuring that the user fees would supplement, rather than replace, federal funding.
I don't think that you will have a lobby of pregnant women because it's different [than pediatrics].

[Is the pregnant population as compelling as the pediatric population? I think the perception is that the pediatric population is more underserved.]

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.

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.

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.

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<th>On Stakeholders</th>
<th>Build Partnerships</th>
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<td>Personally I'd like to see partnerships between a group like the NIH, industry and maybe even third-party payers, to supporting this effort.</td>
<td>Mitigate the risk by building better relationships and partnerships for a trial.</td>
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<td>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.</td>
<td>Share responsibility for public health for 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.</td>
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Key findings for Question 8:

Participants in the study seemed to think 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 Finding #8a. The participants in this study believe that it would take much work on the part of many stakeholders for pregnant women to participate in clinical research.
Key Finding #8b. 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 #8c. Company indemnification should be included when considering all the potential solutions to improving knowledge of pharmaceutical therapy for pregnant women.

Key finding #8d. Patent extensions and transferable extensions should be considered cautiously due to negative industry and public perception.

Key finding #8e. Stakeholders within and external to the pharmaceutical industry have suggestions on how to improve the inclusion of pregnant women in clinical research.
**Question 9. Alternative Methods**

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?

"Could we do better at collecting the data from pregnant women who are taking drugs that are on the market? I'm sure we could."

Interviewees were able to articulate alternative methods of obtaining pregnancy exposure data – many of which are currently being used to some extent, like spontaneous reports and pregnancy registries. Most focused on methods in the post-marketing environment – after the drug is approved and on the market – because of the higher comfort level with pregnant women using drugs whose safety and efficacy is more well-established. Some of the interviewees also suggested making better use of opportunities to gather information from women who become pregnant during clinical trials. One conceded that, "Clinical studies alone may not be adequate, particularly for chronic exposures."

**Pre-clinical:**

As discussed earlier (see responses to Question 6), interview participants believed that more could be done during animal testing to obtain data on the pharmacokinetics and pharmacodynamics of compounds in the pregnant state. Also, it was suggested that new modeling techniques should focus on the difficulties of getting information on the effects of exposure in pregnancy. One participant said, "You have, increasingly, modeling of various types. I guess you have animal models to some extent. None of those are really adequate substitutes but that work goes on now."
Capitalizing on opportunities during drug development:

Several of the interviewees thought that inadvertent pregnancy exposures during clinical trials are a potential source of data that we have traditionally neglected. One participant asked, "Do we need to change our approach to inadvertent pregnancies in clinical trials in order to capture data?" Many shared her opinion that "we maybe don't do as good a job as we should in taking advantage of the circumstances."

Others agreed and added that it's not only an opportunity to collect safety data, but it's also "an opportunity to possibly gain some PK data. I think it's a clear opportunity and the more you get prepared for it the more likely you can take advantage of it." This statement suggests that the expectation should be that some inadvertent pregnancies will occur during the study – and the protocol should include a procedure to follow when an exposed pregnancy is diagnosed. Are there pre-exposure blood samples that can be compared to early-exposure blood samples at different gestational weeks of exposure during the pregnancy – whether or not the woman is maintained in the trial? This is valuable information that would be very difficult to obtain outside of a clinical study.

A physician suggested, "If a woman becomes pregnant in a clinical trial, we can "ask her if she would volunteer to be in a pk study, as a voluntary thing, not a mandatory thing. 'Would you mind giving us a sample of your blood? Just to know how much of the medication we should give you.' That would be such an amazing source of information."
Currently there is no mandate that a woman who inadvertently becomes pregnant during a clinical trial is discontinued or continued in the trial. Most, however, are immediately disenrolled. "I think the withdrawal instruction is pretty strong," said one participant, but added that "you can readdress restarting the drug" as an exemption to the protocol on an ad hoc basis following appropriate analysis and agreement from the PI, the Data Safety Monitoring Board, the IRB, and the Sponsor. But, whether their condition warrants staying in the trial, many interviewees agreed that the pregnancy – which has likely been exposed for several weeks – should be followed to outcome.

"Following a pregnant women from clinical trials is not mandatory. So that's the first thing that I think all companies should do - that the woman was pregnant in the clinical trials, even if she gets excluded from the trial, from now on they should be followed up to know the outcome. That's rule number one" advised a pharma company physician.

Said another, "Right now, we're missing, we lose that data, we're not following it. I'm sure you've been in conversations over the years at the company where the argument is... 'well, yes, we might have them, but we're only going to have four, five or six. We can't do anything with that data, so we're not going to collect it.' And I think we have to change that mindset, appreciating fully that you can't use traditional kinds of analysis on four, five or six, but that information is important."
However, another participant cautioned, "What is probably difficult to expect industry to swallow, would be some sort of commitment to follow-up a child for the rest of its life…"

**Post-marketing surveillance:**

"Could we do better at collecting the data from pregnant women who are taking drugs that are on the market? I'm sure we could."

Once the product is approved and goes onto the market, there are further opportunities to identify and capture pregnancy-exposure data. "It becomes a pharmacovigilance issue. I think this whole thing probably fits better in pharmacovigilance that it does in drug development," said one participant. Suggested another, "Perhaps doctors who are treating their patients might be willing to voluntarily submit data - with the patient's permission because of HIPAA⁵ - but maybe through some sort of, it's not really a trial but some sort of process could be developed. ...At least they could have sort of a databank of data that they could refer to that could be analyzed, perhaps data that could be open to them to also receive." Current voluntary reporting of exposed pregnancies is thought to be very low.

A relatively new (2002) FDA requirement for industry is the mandate to include a "Risk Management Plan" (RMP) in the drug approval application. The RMP must include a section addressing 'special populations' which includes pediatrics, geriatrics, and pregnant women. In it, the company must address how the company plans to monitor the use and safety of the drug in these populations. To monitor use in pregnancy, such steps could include special

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⁵ [http://www.hhs.gov/ocr/privacy/hipaa/understanding/special/index.html](http://www.hhs.gov/ocr/privacy/hipaa/understanding/special/index.html). HIPAA (the Health Insurance Portability and Accountability Act) includes an exception for the reporting of safety surveillance data – the patient's permission is not required because of the value of spontaneous reports to protecting the public health.
clinical studies, epidemiologic studies, and enhanced or routine surveillance. One interviewee stated that, "I think the Swedish pregnancy registry and the Merck pregnancy registries are great ideas, great programs. I think that in risk management plans they should always be included."

On the topic of pregnancy registries:

Pregnancy registries was the most frequently cited method of collecting pregnancy exposure information, "The registry is the primary way to systematically collect that information" said one participant. Said another, I feel as though it should almost be like, 'why shouldn't you do a pregnancy registry?' instead of like, 'you're going to have to do a pregnancy registry.' 'It should be the minimum.'

There are different types of registries – population-based registries like the Swedish Medical Birth Register; company-based pregnancy registries like those run by Merck and other pharma companies, including collaborative registries like the Antiretroviral Pregnancy Registry in which multiple companies are involved; and independent registries run by academic medical centers, like the Anti-Epileptic Drug registry or teratogen information hotlines, like the Organization of Teratogen Information Services (OTIS) for certain diseases or drugs.

The study interviewees had various experiences with pregnancy registries. Said one, "We've done a few nice little observational studies using the Swedish registries where for the cost of some statistical help, the registries are all available."
Another said, "...there was a pretty good study from one of the teratology consulting groups, from Israel but part of a European group, where for every women who called in with a question about an ACE- inhibiting drug they'd say, 'okay, we have a study, we would like to follow you long-term,' so they began filling out the forms and created it. That's a relatively inexpensive way to collect some long-term or at least pregnancy outcome data with people who self identify."

Other participants described some of the registries' limitations, "The trouble is, [registries] ...take more time than, say, if you did a clinical trial. The difficulties with registries ...are, of course, identifying the patients, making sure they get enrolled in the registry, getting the results into the registry and so forth. I guess the question would be, do you think that they get the data in a timely enough manner or that a trial would get... the data probably a little earlier".

Other limitation were cited, "It's unfortunate....that it's a teeny tiny fraction of the women who are exposed to a particular compound, actually register. Even then only a subset of them are actually followed to the conclusion of the pregnancy so I think better use of the registry approach would be a great thing."

Another idea generated by a study participant was the use of the pregnancy registry methodology – studying pregnant women who self-identify or who are reported by their health care provider in the post-marketing environment – for a pk study. He suggested, "[W]e
could have the Phase IV trial, ...a single arm kind of trial. I would prefer to call it a study rather than a trial. For example, you could establish a pregnancy registry or surveillance program... and when women call up and say I just became pregnant, we can ask, 'would you like to be in a study where we will take one [blood] sample? In exchange, we will do a checkup for your baby, or we will take a picture of the baby for you and it will be framed, or a magnet for the fridge,' and then if they accept that - the context is you are already a registered participant who wants to volunteer, that's what I would do for those PK studies. We know that we don't need to have hundreds of women for these studies, a few women and you can do the entire study. I would do it in the context of a pregnancy registry or surveillance program, only those voluntary studies."

So the pregnancy registry appeared to be an accepted means of obtaining safety data – albeit with some room for improvement.

On the topic of epidemiological studies:

In addition to a pregnancy registry, participants suggested other studies in the post-marketing environment utilizing electronic medical records or other databases containing information on pregnancy drug exposures and pregnancy and fetal outcomes. They suggested that this is an emerging field where possibilities for improved data capture and analysis are being developed.

A company physician stated, "I would use the spontaneous reports to see if there's an issue and only if the spontaneous reports are suggesting something, would I then try to design
either a registry or an observational study - because they're a lot of work unless you know
what you're looking for." Another suggested to "do a large database study using electronic
medical records to identify what drugs are taken and what congenital anomalies are
identified, but they're not easy to do and they're not cheap to do."

**Regulatory agency support**

One of the interviewees, a physician who had worked at several pharma and bio companies
expressed frustration with a lack of attention to the issue within the companies. She
suggested both an increase in sensitivity and knowledge within the companies and requested
assistance from the regulatory agency on data review and analysis. She said, "I was seeing
signals and I would take it to our safety review team meetings at [the company], and
everyone was, "no." They really were quite dismissive because these are all small studies. So
I think being able to have people who are in the companies who are educated with regard to
pregnancy and pregnancy data and how to get pregnancy data. And trying to standardize the
review, getting not just the companies reviewing the data. I'm getting to feel as though it's
very ad hoc at the moment, the way we approach pregnancy. Maybe there could be a
standardized way of looking at pregnancy data, especially from a post-marketing point of
view. Some guidelines like that. When is there a safety signal that you should be doing more?
Does it have to be statistically significant or what? That kind of stuff."

The FDA interviewee thought the proposed changes to the pregnancy section of the label,
which have been in development for over 10 years now, might be helpful. She said, "The
Pregnancy and Lactation labeling rule, when it appears, will have a greater emphasis on
human data when it's available and hopefully a better mechanism to get that human data into the label. Having that rule out, that regulation out, might have an effect on this issue because [having] a better mechanism to get it into the label, it may make people more willing to capture that data in a systemized fashion."

**Question 9b.** Do you think a pharmaceutical company would support fund this kind of research? Why or why not?

"[T]he FDA draft guidance...may be the tipping point on this."

Most participants expressed the opinion that companies should fund these kinds of studies – "I think it's the responsible thing to do on the part of the company" -- if only as an alternative to the more costly process of conducting a clinical trial - "...it's a smaller investment to invest in the registry or a databank than to invest in a clinical trial that they don't want to take responsibility for." But there were mixed sentiments about whether or not the funds would actually become available.

"Would a company fund this kind of research? I think it depends on the pharmaceutical company. From my experience it's very difficult to get that funding. Because once again it's were back of that old mindset of we don't really want to know because nobody really seems to care about this so why do we care about it?"

"There's got to be a large perceived need for the information. I think everyone acknowledged with HIV - where we were looking at multiple companies and NIH and others were looking at
maternal-fetal transmission, so there was a clear need. I think there has to be a clear need in order to make the companies jump for that. Where there's a perception that we already meet that need - you can give insulin for diabetes in pregnancy - it's a little less interesting for us to do a major new study for products for treatment of diabetes in pregnancy when they already have an available therapy."

A couple of the interviewees felt that input from the regulatory agencies could be helpful in encouraging companies to conduct and fund these studies or programs.

"I think [companies] would when influenced by regulatory agencies. They would, particularly when pressed upon by the regulatory agency. The H1N1 study we did...was done because the [regulatory agency] wanted the company to do it. So it's clear that the regulatory agencies are requiring more and more post-authorization efficacy and safety studies. So I think it does require the regulatory agency really asking you to do it because it takes a lot of resources to do it properly."

One participant concluded, "I think once the FDA draft guidance comes out, it's going to prompt a lot of thinking in this area. And that may be the tipping point on this."

**Key findings for Question 9:**

Study participants proposed that there are opportunities available to improve our current capture of pregnancy exposure data from pre-clinical modeling to post-marketing spontaneous reports. Many felt that, even if studies are conducted during pregnancy, data
should continue to be collected and monitored throughout the lifetime of the product.

Obtaining industry support for funding such efforts was seen as a barrier to their adoption. Public advocacy and regulatory pressure were perceived as potential solutions.

**Key finding #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.

**Key finding #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.

**Key finding #9c:** Pharmaceutical company 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.
Question 10. Ethics

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?

"You've got disenfranchised women basically. They're truly disenfranchised."

The study participants expressed a number of concerns regarding the ethical issues raised by the subject matter of the interview. Traditional medical ethics – non-maleficence, justice, and autonomy – were raised, along with a suggestion that perhaps feminist ethics would make a contribution to the debate. They mentioned their struggles with issues raised by the concept of including pregnant women in research including society's uneasy relationship with fetal protection, including the abortion debate, 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?

Ethics

One company physician commented, "I think that we overplay that card" in reaction to the usual response when this issue is raised, which is, "we can't ethically include pregnant women in clinical research." In contrast to that response, several interviewees stated that it is unethical not to include pregnant women in clinical research; "Incorporating pregnant

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women is the right thing to do, we should include them from the ethical aspect" and "this is just the simple humanity..."

In speaking to this study's participants, I found the IRB representatives to be most comfortable in discussing ethical principles, followed by company physicians. The vocabulary of medical ethics was raised by one IRB employee, but countered by a company physician who felt that the industry does not pay enough attention to ethical principles. In contrast, in response to the question, 'what ethical problems are raised…' a company lawyer responded, "Nothing comes to mind."

"The Belmont principle is the lingua franca for day-to-day operations of ethics in human subject research. It's the framework around which the regulations are written for sure, and the guidelines. So I think the specific ethical issues are probably most readily accessible in that language. You can ask questions of whether other ethical perspectives, for example feminist ethics, which I'm not deeply into, but I hear as being largely an ethic that emphasizes care as opposed to what is seen as more coldly rational application of principles and precepts. Feminist ethics might have a take on this but I'm not competent to suggest what that take would be."

But, said the physician, "Companies don't often think in ethical terms, most of them don't understand ethics or bioethics, so even a well articulated argument goes over their heads. I don't think there's an easy answer - that's a long-term question of trying to improve the knowledge of ethics and bioethics in the population - in business and in medicine."
Another physician named the most commonly invoked principles in this debate: "You've got autonomy, primum non nocere, and distributive justice. The question of autonomy and the question of harm are on one side, on the other side you've got distributive justice."

Non-maleficence

"I think that 'do no harm' is the biggest thing that researchers and physicians face. Do no harm. No one wants to do any harm." This principle, above all the others, was the one most consistently invoked by the study participants. However, further exploration of the topic revealed the common understanding that clinical research has inherent risks of causing harm. Stated one participant, "I don't believe... that we can't do it because of an ethical possibility that we may cause harm in people. Everything we do may cause harm in people." And once it was established that, of course, no one want to do anyone any harm, the conversation could progress to discuss potential ways to do research with pregnant women that lessens that risk – as is done for all populations that participate in research.

Autonomy

Of course, discussing ways to reduce risk assumes that pregnant women are given the opportunity to participate. At this point in time, as one interviewee stated, "You've got disenfranchised women basically. They're truly disenfranchised." Not allowing pregnant women the opportunity to potentially improve their medical condition and potentially contribute to generalizable medical knowledge, violates their autonomy - the first principle of
the Nuremberg Code,\textsuperscript{6} and the Belmont Report.\textsuperscript{7} (See Chapter 3. Ethical Framework).

Essentially, the pharmaceutical company is making the decision not to participate for them. But, counters a company physician, "we make those kinds of decisions all the time" in our inclusion and exclusion criteria. Pregnant women would be no different from elderly patients or patients with renal impairment who are not included either. At which point the question becomes, if patients in initially excluded populations will potentially have need of the drug in development, will those studies be done, and if so, when?

**Informed consent of the mother**

One of the ways that clinical research deals with risk in clinical studies is by ensuring that the benefits and risks known at the time of the study are articulated in the informed consent document and shared with potential participants in a manner in which they can understand the contents. This process allows the potential study subject to practice his or her autonomy by making an informed decision about whether or not to participate. Several interviewees stated that the informed consent process is very important to their belief that the clinical study is being conducted in an ethical manner.

"My ethical position is very simple. I think as long as the people are adequately informed with informed consent and a good discussion, I personally, am in favor of conducting studies in these populations because they do benefit from them and these are important studies that need to be done."


\textsuperscript{7} The Belmont Report, available at \url{http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html}; accessed 05May2011.
"I think being able to share with [pregnant women] what you do and do not know about the drug with them [is important]. Because at the time that you do this study, you have to say to them that we don't have any data in pregnant women. That has to be told to them and that's why we're doing the trial, to get this information, and you are being helpful."

Another participant explained that we need to have gathered as much information as possible regarding benefits and risks prior to conducting the study so as to "lay out clearly for folks that these studies are being done at a point where we have relative confidence on risks so that there's no perceived undue risk because of unknown data."

**Informed consent of the fetus**

An issue that was raised by several interviewees, and especially by the IRB participants, was the question of the pregnant woman giving consent for the fetus. States one participant, "I think the biggest ethical challenge, one of the main reasons why an IRB or Sponsor wouldn't want to conduct research on pregnant women, is that now you don't just have the woman, you also have the fetus. ...I think the ethical concern is you could potentially be making a decision for two people." In addition, she added, "Does the father also need to provide consent in this situation or is that encroaching on the mother's autonomy to make her own decisions? So I think there's going to be a lot of concern and confusion over really whose decision is it to enroll in the research."

Other participants strongly disagreed with this assessment. Said one company physician, "I think we have similar situations all the time in clinical trials - for instance, Alzheimer's
patients. There's a lot of study being done on Alzheimer's patients because there's really no medications out there for them, so it's usually the caregiver that gives the informed consent, because the patients can't give it. And in my experience with Alzheimer's trials, because there's nothing out there to treat it, the regulatory agencies and IRB's are willing to approve drugs - I mean investigational products that do have significant side effects. So if you look at an Alzheimer's program, in my view they haven't given consent, they're having severe outcomes from the study drug. So I mean, don't we do this all the time already?"

The FDA participant summarized her frustration with the issue stating, "I think we're going to have to get over and put away the issue of consent."

**Distributive justice**

One of the study participants described the issue of distributive justice in this way, "When you're talking about ethical considerations, in the Belmont Report, one of the three principles is justice. You need to have an equal distribution of the benefits and the burdens of research. If you're not testing pregnant women you don't have equal distribution of the benefit of the research."

An IRB employee agreed, "Pregnant women are entitled to be considered in research because it's their right. They're like anybody else. If you're going to exclude a portion of your population from research you have to have a good rationale for it. Like if you're going to conduct a study and you're going to exclude African-Americans, well why? Why would you do that? They're entitled to bear the burdens and the risks as well as the benefit of whatever
else is out there." As long as, she added, "the benefits of participating in the research...always outweigh the risks."

Finally, a company physician, with an awareness of the history of the development of clinical research in this country, stated, "I agree with AIDS activists and women who want to know the answer to the question."

**Society, the fetus, and abortion**

As discussed in previous chapters, there is an uneasy social consensus on the status of the fetus as a person/patient in its own right or as an entity that is wholly dependent on its pregnant mother. Several participants saw a conflict between the pregnant woman's benefit/risk considerations and the fetus' benefit/risk considerations. "From a pure bioethics standpoint, there is a diversion between the risk to the mother and the risk to the fetus. [There's] no social consensus – that may be the reason for the risk aversion," stated an industry professional group lawyer. But, he acknowledged, "there is not always a conflict between the two." Another participant barely acknowledged this in a similar statement, "The question here is also the generic ethical question of weighing benefit/risk to a mother against mostly or almost exclusively risk to a fetus. Almost exclusively because improvement in pregnancy outcome by treating a disease is certainly a benefit to the fetus so you have to ask the question that way."

In a similar vein, the topic of abortion, though not explicitly raised by the issue itself, was implicitly surmised by some of the interviewees. "I don't know, it shouldn't, but I suspect it
will raise the issue of pregnancy terminations as well, and how women get counseled on that," said one. "You're going to have the major ethical concern, you're going to have board members on the IRB of various different backgrounds and beliefs and different beliefs on abortion as well. So I think another major ethical concern, depending on the board member, is whether or not it would be appropriate, whether to test something that could be harmful not only to the mother but also to the fetus," said another. A third interviewee said, "[P]eople debate over whether the fetus - and about the whole abortion debate about the fetus - I think that's the biggest ethical concern." In this regard, I think it is important to know that concerns about abortion could influence participants' considerations and decisions in debates about the inclusion of pregnant women in clinical research. Such concerns may need to be directly addressed in proceedings on the topic.

**Corporate Responsibility**

Study participants were sometimes prompted by me to consider the issue of industry's contributions to the good of society vs contributions to their shareholders. How is the need for improved knowledge about how to treat pregnant women reconciled with the costs and risks to the companies? There were mixed responses to this question, some responding that a company's primary concern is to make money:

"You can ask if there some kind of an ethical requirement borne by the industry that goes beyond the normal operations of business ethics. I would say strictly speaking, no. That is, I find the notion of the pharmaceutical industry duty to care to be rather elusive to say the
least. You can, at times, construe the pharmaceutical industry as a branch of medicine, which it's not."

"I don't think that [corporate responsibility] holds enough weight compared to risk. So I personally would want to see protection for the sponsor and the investigator for enrolling women who are pregnant to offset that perceived issue of fairness. I think fairness - fairness has a role in non-profit government-sponsored research. I think it's a little different in a private sponsor conducting research. Conducting research, we make all sorts of decisions about who we want our initial target population to be, what we're pursuing and not pursuing etc. I'm not sure that argument holds enough weight considering the risk of enrolling pregnant women early on."

And finally, from a company physician, "I have become very cynical over the years. I personally think pharmaceutical companies are in it 99% for the money and the rest of it is just a show. Okay, great, we've got a drug for X, and yes, it does help a lot of patients, but the best part of it is, 'look at all the profit we made!' And we've made Wall Street happy. Wall Street drives Pharma. I think that Pharma is very well regulated. You have safety physicians, you have governance, strict governance to ensure patient safety. People think we make patients lives better and that's great and all, but in general, the reason why pharmaceutical companies work is because of the profit, to make profits, as Wall Street drives the capitalistic system. So I think in general, you're not going to get companies to do this unless there's something in it for them or there's some sort of guidelines or guidance saying it's important
to do this - then maybe... I know that's a bit harsh. But once people realize that, once people realize that this is a big unmet need in today's society, maybe that will help. But it's difficult."

On the other side of this question, many of the interviewees articulated a commitment to providing effective and safe treatment to patients as a high ranking corporate responsibility:

"My personal feeling is that we do [have responsibility to our patients] and that's why you and I and many others are in this business. I guess we like to see the company be successful and pay the stockholders but I think the opportunities to do studies that have significant public health benefits are really no longer in many other people's hands. I think to some degree the pharmaceutical industry is standing alone in this anymore. Even the National Institutes of Health studies that they do on diabetes and other outcome things, basically we donate the drug. They're basically dependent on the pharmaceutical industries even to support their public health focused studies."

"I think one thing is clear. We have the ethical responsibility to give the best evidence that we can about the use of our drugs by the populations which may be using them, whether or not that's technically an approved population or not. So if we know that every woman getting a urinary tract infection during pregnancy is using our drug, I think we have an obligation to be real clear about the impact of pregnancy on this drug."

"We know that our drug is being used in pregnancy but we close one eye to it, we'll take your money, thank you, but we don't want to go there? I think that's our responsibility."
To further the discussion, participants sometimes offered reasons for some companies' reluctance to include pregnant women in research and suggestions on how to improve the situation:

"Why exclude [someone] from something that benefits them? [Because there's] not a strong enough driving factor to enroll them. The upside is not very clear. You'd have to shift the mindset, the tone at the top of the Company with maybe a regulatory guidance to push endorsement. I am less aware of patient advocacy groups for this population than there are for other disease-related organizations or for the pediatric population. I think it would be hard to change that mindset. An agency guidance would be persuasive - but they'd have to duke it out with the lawyers. In this environment, the bottom line is important."

Others raised the belief that doing what is right is good for the company:

"I think that potentially it could give the company a very good name if you do it well. A company that is working well with...the regulatory agency, in terms of the regulations and having things in place. It gives the people the impression that these companies are doing a good job, they have really taken care of the situation - pregnant women and breast-feeding women - that it's a very good impression. That's the company that I trust.....[B]ecause, look at this company, they're doing a pregnancy registry, they are doing the study, they have the know-how. It gives you a little bit more security when you use the drug. Now, obviously people go for the price nowadays, but in your mind, if the company is putting these things in
place, you kind of trust the company more. So instead of being a cost, you can see it as a perception you give people who are potentially stakeholders that the company is really doing the right thing in safeguarding or placing safety as a priority and it's a trustable company. The company will get more bottom line and then the shareholders will see that and will invest in the company."

Key findings to Question 10:

Key finding #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.

Key finding #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.

Key Finding #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.

Key finding #10d: While most participants felt that pharmaceutical companies had a responsibility to provide safety and efficacy information for products that would be used by pregnant women, many also acknowledged that business considerations 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 such decisions.