Pregnant women and their fetuses deserve timely access to safe, effective, evidence-based care. To this end, pregnant women should be included in clinical trials of drugs and vaccines, except when there is a compelling scientific or ethical reason not to do so. This article examines the benefits and limitations of two different starting points for research involving pregnant women. The first option would have stand-alone Phase I trials for pregnant women initiated at the same time as Phase III trials in the general population. The second option would have Phase I trials for pregnant women embedded into late Phase II or Phase III trials, with enhanced monitoring for pregnant women, similar to that done in a stand-alone Phase I trial.

“*If we consider the availability of a drug proved to be safe and effective through the devices of modern clinical pharmacology and clinical trials a benefit, then it is unjust to deprive classes of persons, such as children and pregnant women, of this benefit*” [1].

More than a decade ago, Emanuel *et al.* asked and answered the question: “what makes a clinical trial ethical?” [2]. They identified seven ethical requirements, one of which was fair subject (participant) selection – that is, fair inclusion/exclusion criteria, as well as fair recruitment and enrollment practices. This ethical requirement, founded on the principle of justice, “holds that particular individuals, groups or communities should neither bear an unfair share of the direct burdens of participating in research, nor should they be unfairly excluded from the potential benefits of research participation” [101]. In the first instance, the ethical concern is with exploitation (especially the exploitation of vulnerable persons). In the second instance, the ethical concern is with equity.

In recent years, with the notable exception of clinical research in developing countries, there has been considerable progress in minimizing the risk of exploitation due to inappropriate inclusion in clinical trials. In part, this is due to the fact that no one seriously disputes the claim that it is wrong to exploit others. Regrettably, there has not been similar progress with respect to the problem of inappropriate exclusion from trial participation. In part, this is because many firmly believe (on beneficient or paternalistic grounds) that it is wrong to include certain classes of persons in clinical trials and thereby to expose them to the potential harms of trial participation. This entrenched belief explains, in part, why the argument for appropriate inclusion in clinical trials has had to be repeated time and again for different classes of persons, be they children [1,3,4], women [5–7,102] or pregnant women [8–12].

It is now widely accepted – in principle, if not always in practice – by researchers, research sponsors, research ethics committees and research regulators, that research involving children and research involving women benefits children and women, respectively. This is not yet the case for research involving pregnant women and their fetuses.
women, but we expect that it will soon be so, given the validity and weight of the arguments in support of research involving pregnant women. Nevertheless, research involving pregnant women is familiar – persons who are not simply miniature adults and healthcare providers should not be treating children on the basis of data extrapolated from clinical trials involving adults. Children cannot be regarded simply as ‘little people’ pharmacologically. Their metabolism, enzymatic and excretory systems, skeletal development and so forth differ so markedly from adults’ that drug tests for the fetus must be conducted in manners likely to maximize “the frequency of scientific or ethical reason to exclude them (e.g., a clinical trial of a sex-linked disease such as prostate cancer). To properly care for children as a class, children should be included in potentially beneficial clinical trials, except when there is a compelling scientific or ethical reason to exclude them (e.g., a clinical trial of a sex-linked disease such as prostate cancer) or pregnancy-specific conditions (e.g., extreme nausea and vomiting or pre-eclampsia), pregnant women should be included in potentially beneficial clinical trials, except when there is a compelling scientific or ethical reason to exclude them (e.g., the research is irrelevant to pregnant women or the trial involves a known or probable teratogen). A second important fact is that during pregnancy women use preventative products (e.g., vaccines), in addition to therapeutic products. With pregnancy, there are substantive immunological changes to the woman’s body to prevent ‘rejection’ of the fetus. For this reason, if vaccines (products that require a well-functioning, intact immune system) are to be used during pregnancy, they must be tested during pregnancy [9,10]. In addition to clinical expertise, the practice of evidence-based medicine (for the delivery of drugs and vaccines) requires external clinical evidence from randomized controlled trials of pregnant women. Physiological differences between men and women affect the manifestation of disease and treatment. women, but we expect that it will soon be so, given the validity and weight of the arguments in support of research involving pregnant women. Nevertheless, research involving pregnant women is familiar – persons who are not simply miniature adults and healthcare providers should not be treating children on the basis of data extrapolated from clinical trials involving adults. Children cannot be regarded simply as ‘little people’ pharmacologically. 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Research involving pregnant women: trials & tribulations

by regulators for some products (e.g., varicella vaccine and acellular pertussis vaccines). However, it is impossible to avoid the causally using registry-derived data, and randomized controlled trials remain the gold standard. Well-designed clinical trials involving pregnant women are essential in order to avoid the underrepresentation or mistreatment of pregnant women and their fetuses. Such trials are also key to promoting fetal safety by reducing the number of pregnant women treated or vaccinated off-label. In this regard, Goldklang et al. reminded us that: "Ironically, the effort to protect the fetus from research-related risks by excluding pregnant women from research places both women and their fetuses at greater risk from untested clinical interventions, and may also result in a dearth of therapeutic options specifically developed for pregnant women".[11] In time, the validity and weight of the arguments in support of research involving pregnant women should hold sway. Once this happens, practical changes will be needed to meet the demands of justice. For example, research ethics guidelines that are silent on the topic of research involving pregnant women, or that merely permit (but do not require) the inclusion of pregnant women in research, will have to be amended. Furthermore, research funding agencies will need to do more to encourage research involving pregnant women and address the funding priority. If these initiatives fail to bring about meaningful change, then governments may need to provide manufacturers with incentives in the form of enhanced patent protection, or they may even need to mandate the inclusion of pregnant women in research.

Making these sorts of changes will require clarity and consistency regarding when pregnant women must be included in research, and when they may justifiably be excluded from research for compelling scientific or ethical reasons. This is a complex and contested issue. One option is to use the US FDA drug use-in-pregnancy information as a guide for the just inclusion of pregnant women in clinical trials (Box 1).[12] For example, using the current labeling system, there is no reason to exclude pregnant women from research involving investigational products that meet the US FDA-assigned pregnancy categories for phase I, II, or III trials. Instead, the manufacturer should be required to conduct clinical trials in pregnant women, including Phase I trials involving pregnant women. These clinical trials could be conducted in a stand-alone Phase I trial. Depending upon the investigational product, Phase III trials can be designed just to look at efficacy and, depending upon the disease, Phase III trials may not include substantial safety monitoring (or the safety monitoring that is included may be for a clinical adverse outcome that does not involve drawing blood). By contrast, late Phase II trials are often large trials that involve some extended safety monitoring. This makes the integration of Phase I activities (to gather safety data) more feasible.

- **Stand-alone Phase I trials** concurrent with Phase III trials

From a conceptual, logistical and regulatory perspective, stand-alone Phase I trials in pregnant women initiated at the same time as Phase III trials in the general population would be the most straightforward and easier to implement at all stages of the clinical trial life cycle. At the conceptual stage, stand-alone Phase I trials in pregnant women would ensure greater clarity in design and review. Stand-alone protocols would be concise and would focus on issues directly related to the safety of the product in the pregnant woman and her fetus. Safety endpoints would be specific for a pregnant population, and would build on what had been learned with Phase I and II trials in nonpregnant adults. Potential concerns identified in these earlier clinical trials were that of particular relevance to pregnant women. Women could be specifically targeted. Also, as appropriate, stand-alone Phase I trials in pregnant women could include a phased enrollment process so that pregnant women in the later stages of pregnancy were enrolled before women in the first trimester of their pregnancy. In any case, unique features relevant to pregnant women, such as counseling about potential harms and benefits to the fetus, could be included in the protocol. The protocols could also be designed to include outcomes of particular interest to this population, such as long-term follow-up of the effects of the product under investigation on the growth and development of the newborn. These measures should satisfy specific regulatory requirements for research involving pregnant women.

Regarding logistics, with stand-alone Phase I trials for pregnant women, it would be advantageous in identifying qualified investigators to undertake the clinical trials and in recruiting participants into the trials. Research sponsors would be able to identify investigators with the requisite interest, knowledge and skills to provide a safe environment for participants (e.g., more skilled in anticipating and identifying problems related to potential complications for pregnant women or their fetuses). These investigators might be located at facilities having specialized infrastructure for the evaluation of pregnant women and their fetuses, and the follow-up of neonates (e.g., fetal assessment units, high-risk obstetrical care and neonatal intensive care units).

Notwithstanding these many and varied benefits, one limitation to stand-alone Phase I trials involving pregnant women is that data from these trials will not be representative of nonpregnant women, and might be used as evidence of the inclusion of women in higher risk populations. Finally, slower enrollment into stand-alone Phase I trials involving pregnant women would not delay the analysis and reporting of data for pregnant women. The data analysis and reporting stage, stand-alone Phase I trials would ensure that data from pregnant women were analyzed and reported separately. In turn, this might have a positive impact on the conduct of research involving nonpregnant adults, by increasing the expectation of gender subgroup analyses of research data for all clinical trials.

Notwithstanding these many and varied benefits, there are limitations to stand-alone Phase I trials involving pregnant women. First, pregnant women are not necessarily representative of nonpregnant women, and yet stand-alone Phase I trials in pregnant women might be used as evidence of the inclusion of women in trials of a specific drug or vaccine. This could reduce the number of nonpregnant women included in the

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Box 1. US FDA-assigned pregnancy categories as used in the drug formulary.

<table>
<thead>
<tr>
<th>Category</th>
<th>US FDA-assigned pregnancy categories as used in the drug formulary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category A</td>
<td>Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).</td>
</tr>
<tr>
<td>Category B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td>Category C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.</td>
</tr>
<tr>
<td>Category D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.</td>
</tr>
</tbody>
</table>

Data taken from [13]

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[104] future science group

Clinical Trial Perspective
Baylis & Halperin

Executive summary

- Fair inclusion/exclusion criteria are a sine qua non of ethical research involving humans.
- Until recently, children and women were routinely excluded from clinical trials and, as a result, they were deprived of the benefits of research and, as well as the benefits of research participation.
- Now it is widely accepted that research involving children and research involving women benefits children and women, respectively.
- A patient population that is still unfairly excluded from research of potential health benefit is pregnant women.
- Pregnant women and their fetuses deserve timely access to safe, effective, evidence-based care. Frequently they do not get this care because their clinicians do not have pregnancy-specific data about safety, toxicity, dosage, side effects and contraindications of drugs or vaccines for both pregnant women and their fetuses. Clinicians do not have these data because of the routine exclusion of pregnant women from drug and vaccine trials.
- Pregnant women should be included in potentially beneficial clinical trials, except when there is a compelling scientific or ethical reason to exclude them (e.g., the research is irrelevant to pregnant women or the trial involves a known or probable teratogen).
- Well-designed clinical trials involving pregnant women are key to avoiding the non-treatment, undertreatment or mistreatment of pregnant women and their fetuses, and promoting fetal safety by reducing the number of pregnant women treated or vaccinated at all.
- Two different approaches to the routine inclusion of pregnant women in research of potential health benefit are proposed. One approach involves staggering stand-alone Phase I trials for pregnant women initiated at the same time as Phase III trials in the general population. The other approach involves embedding Phase I trials for pregnant women in the late Phase II or Phase III trials, with enhanced monitoring for pregnant women similar to that done in stand-alone Phase I trials.
- The benefits of the first option include: (i) greater clarity in the design and increased ease in the review and monitoring of the clinical trial because only pregnant women are included in the trial; (ii) the use of safety end points that are specific for pregnant women and that build effectively on the knowledge gained from previous trials in non-pregnant adults; (iii) the option of phased enrollment so that pregnant women in the later stages of pregnancy can be enrolled in research before women in the first trimester of their pregnancy are enrolled; (iv) increased probability that there will be planning for counselling regarding potential risks for the pregnancy; (v) increased probability that there will be planning for long-term follow-up of newborns; (vi) greater ease in recruiting qualified investigators and trial participants; (vii) the possibility of reduced liability issues and (viii) timely analysis and reporting of data from pregnant participants.
- The benefits of the second option include: (i) full integration of pregnant women into the clinical research and regulatory approval processes, which clearly signals the importance of normalizing the inclusion of pregnant women in research; (ii) involvement of investigators who are familiar with the protocol as they will have participated in earlier research phases with non-pregnant adults; (iii) reduced start-up costs and monitoring requirements; (iv) enhanced recruitment of pregnant women who will be able to provide research data to the entire population, as pregnant and non-pregnant participants would be drawn from the same population; (v) the ability to provide pregnancy-specific data sooner than would be possible with stand-alone trials because the subgroup analysis could be given priority; (vi) enhanced reporting of gender-specific analyses among non-pregnant research participants and (vii) potentially enhanced statistical power.
- Each of these approaches would be scientifically valid and meet the ethical imperative to include pregnant women in research. In the near future, we expect that stand-alone trials may be preferred by researchers, research sponsors, research ethics committees and regulators, whereas the embedded trials, ultimately, may become the preferred approach.

Two options for the inclusion of pregnant women in research have been proposed: stand-alone Phase I trials to begin at the end of Phase I trials, all sites to enroll pregnant women. How, however, this practice could give rise to other difficulties if the number of sites enrolling pregnant women was sufficiently low as to limit the generalizability of the data. Finally, including pregnant women in late Phase II or Phase III trials might delay availability of data from the overall population if preg- nant women were enrolled at a slower rate than non-pregnant adults.

Conclusion & future perspective

Two options for the inclusion of pregnant women in research have been proposed: stand-alone Phase I trials to begin at the end of Phase I trials, all sites to enroll pregnant women. However, this practice could give rise to other difficulties if the number of sites enrolling pregnant women was sufficiently low as to limit the generalizability of the data. Finally, including pregnant women in late Phase II or Phase III trials might delay availability of data from the overall population if pregnant women were enrolled at a slower rate than non-pregnant adults.

Executive summary

- Two different approaches to the routine inclusion of pregnant women in research of potential health benefit are proposed. One approach involves staggering stand-alone Phase I trials for pregnant women initiated at the same time as Phase III trials in the general population. The other approach involves embedding Phase I trials for pregnant women in the late Phase II or Phase III trials, with enhanced monitoring for pregnant women similar to that done in stand-alone Phase I trials.
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Clinical Trial Perspective

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Websites