

Research involving pregnant women: trials and tribulations

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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.

Keywords: clinical trials • fetuses • inclusion/exclusion criteria • pregnant women
• research ethics • trial design

“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 beneficent 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, but we expect that it will soon be so, given the validity and weight of the arguments in support of such research. When this day comes, a number of practical ethical issues

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will come to the fore, including issues of trial design, risk perception in prospective participants' assessments of the harm–benefit ratio, informed consent, the right to withdraw, liability and indemnification.

This article focuses on trial design and examines the benefits and limitations of two different approaches to the routine inclusion of pregnant women in research of potential health benefit – one approach involves staggering, the other embedding. With the first approach, small, well-designed Phase I safety trials for pregnant women would begin at the same time as Phase III efficacy trials in the general population. In this way, trials involving pregnant women would only be initiated once the investigational product had successfully completed Phases I and II in men and nonpregnant women. With the second approach, pregnant women would join late Phase II or Phase III trials once the investigational product had passed safely through Phase I and at least early Phase II in men and nonpregnant women. The participation of pregnant women in these trials would be identical to that of men and nonpregnant women, except for the enhanced monitoring of pregnant women, similar to that done in Phase I trials. With this second approach, the pregnant women would do 'double duty' insofar as they would generate both safety and efficacy outcome data. There would be the Phase I outcome data from the additional intensive safety monitoring, as well as the outcome data for the late Phase II or Phase III trial.

To be clear, while this article reviews some of the arguments in support of research involving pregnant women, it does not focus narrowly on the question: 'why should pregnant women be included in clinical trials?' In the interest of advancing changes in policy and practice, this article also focuses on the downstream question: 'how should pregnant women be included in clinical trials?' Without a workable answer to this question, the research, regulatory and wider community will not act on the ethical obligation to routinely include pregnant women in research, except when there is a compelling scientific or ethical reason to exclude them.

Research involving children & women

Two of the arguments presented in support of research involving pregnant women are familiar – persons should not be unfairly excluded from the benefits of research, nor should they be unfairly excluded from the benefits of research participation. In the recent past, these arguments have been advanced successfully in support of research involving children and research involving women. A brief summary of these arguments is provided below for illustrative purposes and to better situate the current research ethics debate about pregnant women in its historical context.

In North America, the argument for research involving children dates back to the 1970s, at which time the proponents of pediatric research insisted that children should not be excluded from clinical trials solely on the basis of age, and thereby denied the benefit of research and research participation. Children 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 latter provide inadequate information about dosage, efficacy, toxicity, side effects and contraindications for children" [3].

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. Such research would generate child-specific data on the basis of which pediatricians could practice evidence-based medicine (i.e., medicine that successfully integrates "individual clinical expertise with the best available external clinical evidence from systematic research") [13]. In this way, pediatricians can best avoid age-specific adverse reactions, ineffective dosing and therapeutic failures that are the result of extrapolation errors [14].

In addition to the benefits of research for children as a class, there are the benefits of research participation for individual children. Children participating in ethically designed and managed clinical trials would be better served than children receiving new drugs outside of a trial who would be exposed to unknown risks in a manner likely to maximize "the frequency of their occurrence, while at the same time minimizing the probability of their detection" [1].

Arguing along similar lines, in the 1990s the proponents of research involving women insisted that women should not be excluded from (or under-represented in) clinical trials solely on the basis of sex or gender, and thereby denied the benefit of research and research participation. Women are not simply men with different hormones and clinicians should not be treating women on the basis of data extrapolated from clinical trials involving 'single white males' [5]. Physiological differences between men and women affect the manifestation of disease and treatment:

"Women are not simply 'men with estrogen', they differ systematically from men in many ways, including in their genetics, metabolism, behavior and social determinants of health (i.e., occupation and socioeconomic position). Female–male health differences may be due to 'sex' (i.e., sex-linked biology), 'gender' (i.e., socially-structured relations) or both" [15].

With regards to sex-linked biology:

“Factors such as body weight, body surface and ratio of lean to adipose tissue can affect optimal doses as can the greater concentration of steroids in mens’ bodies, the differences in hormones, the use of artificial hormones by women (for birth control, control of menopausal symptoms and fertility treatments) and so on. Focusing on one type of human physiology [that of men] reduces the generalizability of the experimental data and thus reduces the scientific utility of the research” [7].

To properly care for women as a class, women 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).

To date, as with research involving children, considerable progress has been made regarding the just inclusion of women in research [16]. Nevertheless, women continue to be excluded from, or under-represented in, certain clinical trials (e.g., cardiovascular disease, cancer and HIV/AIDS) [17]. There are many reasons for this, but salient among them is fear concerning the risk of harm to the developing fetus (e.g., the risk of miscarriage or birth defects) if women research participants become pregnant [15]. This concern means that few drugs are developed for conditions that occur during pregnancy [18] and women are often excluded or under-represented in clinical trials, not only on the basis of sex and gender, but also on the basis of reproductive capacity, pregnancy and lactation.

Research involving pregnant women

As Lyerly *et al.* argue authoritatively, research involving pregnant women is necessary to provide women with effective treatment during pregnancy, to promote fetal safety (e.g., by avoiding the clinical use of drugs that may be harmful to the developing fetus), to reduce the harm of suboptimal care, due to reticence on the part of physicians to properly prescribe potentially beneficial medication and to provide pregnant women and their fetuses with access to the benefits of research participation [8].

Not surprisingly, some of these arguments rehearse familiar aspects of the arguments for the just inclusion of children and women in research – pregnant women should not be excluded from research solely on the basis of pregnancy, and thereby denied the benefits of research and research participation. This time, the opening salvo is that pregnant women are not just women with bigger bellies. Physiological changes during pregnancy, such as “increased plasma volume, body weight, body fat, metabolism and hormone levels” preclude the extrapolation of data about dosing and safety (from men and nonpregnant women) to pregnant women [9].

“Pregnancy extends and alters the impact of sex differences on absorption, distribution, metabolism and excretion of drugs – often in ways that are both dramatic and difficult to predict. Pregnancy-related changes in the gastrointestinal tract, cardiovascular system, kidneys and other organs may profoundly alter the way that drugs are processed by the body (pharmacokinetics) or the way that drugs act on the body (pharmacodynamics)” [8].

The fact is that “pregnant women get sick, and sick women get pregnant” [9]. In either case, for clinicians to provide these women with appropriate and effective care, they will sometimes require pregnancy-specific data about safety, toxicity, dosage, side effects and contraindications of drugs for both pregnant women and their fetuses. Preclinical toxicology and teratogenicity data and animal models are useful and required by regulatory authorities, but they do not reliably predict adverse affects in humans [19]. To properly care for pregnant women with pre-existing medical conditions (e.g., chronic hypertension and diabetes), medical conditions that can arise during pregnancy (e.g., psychiatric illness, cancer and autoimmune disease) or pregnancy-specific conditions (e.g., extreme nausea and vomiting and 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 [20,21].

In addition to clinical expertise, the practice of evidence-based medicine (for the delivery of drugs and vaccines) requires external clinical evidence from research. Treatment registries of postmarketing use of products off-label can be useful in identifying safety signals in pregnant women, and have been required by regulators for some products (e.g., varicella vaccine and acellular pertussis vaccines). However, it is impossible to ascribe causality 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 nontreatment, under-treatment 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, Goldkind *et al.* remind 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 unstudied 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 identify research involving pregnant women as a 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) [103]. For example, using the current labeling system, there is no reason to exclude pregnant women from research involving investigational products that meet the description of category A or B drugs. In sharp contrast, there may be every reason to do so for investigational products that meet the description of category X drugs. The complicated categories are C and D. With these categories, depending upon the stage of pregnancy (e.g., first vs third trimester), the dosage and the anticipated benefits for pregnant women and their fetuses, there may or may not be compelling scientific or ethical reasons to exclude pregnant women from clinical trials. In the near future, the FDA may change the current letter-based requirements (this was proposed in 2008, but as yet no changes have been made [104]). If changes are made, future labeling requirements for the use of prescription drugs during pregnancy may be equally useful as a guide to the just inclusion of pregnant women in research. If not, there is no principled reason not to use the current descriptive categories in identifying trials that should include pregnant women.

With the requirements for research involving pregnant women in place, researchers will have to find effective ways to routinely include pregnant women in research. Two options for the effective inclusion of pregnant women in clinical trials have been proposed.

These are:

“Small, well-designed trials for pregnant women, starting with Phase I safety trials that would begin at the same time as Phase III efficacy trials in the general population. With this staggered approach, pregnant women and their fetuses would not be exposed to any compounds that failed in Phase I and II trials. Another option would be to allow pregnant women to join Phase III trials once a drug has passed safely through Phases I and II. This would need to include enhanced monitoring for pregnant women, similar to that done in a stand-alone Phase I trial” [9].

We list the benefits and limitations of each of these options below, with a minor amendment to the second option allowing Phase I trials involving pregnant women to be embedded into either late Phase II or Phase III trials. We propose this amendment because with some Phase III trials it might not be practical to embed a 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 easiest 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 end points 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 that were of particular relevance to pregnant 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 addition, 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

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

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).

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C

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.

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or 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.

Data taken from [103].

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 there would be advantages 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 would likely be located at facilities possessing 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). In addition, the specialized nature of stand-alone Phase I trials might assist with the recruitment of pregnant women by promoting an atmosphere of special care, attention and concern for monitoring the safety of pregnant women and their fetuses.

The selection of clinical trial sites could take into consideration different cultural and national attitudes toward research in pregnant women. Locations where research in pregnancy had not yet achieved public or regulatory acceptance could be avoided. Liability issues might also be reduced with stand-alone Phase I trials in pregnant women, since optimal sites would be obstetrical centers already insured for interventions 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 in nonpregnant populations.

At 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 Phase I trials. Second, slower enrollment into stand-alone Phase I trials might delay the availability of the product for pregnant women relative to the general population. Third, for any number of reasons, the stand-alone Phase I trials in pregnant women may never be initiated. And finally, the benefits of embedded Phase I trials (described below) highlight additional limitations with stand-alone Phase I trials.

■ Phase I trials embedded into late Phase II or Phase III trials

Embedding Phase I trials involving pregnant women into late Phase II or Phase III trials in the general population would provide the highest degree of integration of pregnant women into the clinical research and regulatory approval processes. This level of integration would send a clear message about the obligation to include pregnant

women in clinical trials, and would help normalize this practice for potential research participants.

With this approach, the late Phase II or Phase III trials would be designed so that the primary outcomes are identical in pregnant women and nonpregnant adults. In addition, the protocol would have differential interventions and additional outcomes for the participants who were pregnant. In this way, the pregnant women in the late Phase II or Phase III trials would not only generate Phase II or III outcome data, they would also generate Phase I outcome data. In addition, the design would require stratified enrollment and randomization, supplementary clinical and safety monitoring and specialized follow-up for those participants in the pregnant cohort.

In terms of logistics, by definition, the same researchers would undertake the clinical trials in both populations so familiarity and experience with the research interventions would be optimized. However, co-investigators with obstetrical experience would need to be added to the research team (at sites where pregnant women would be enrolled) to enhance expertise. New infrastructure would not be required as the embedded pregnancy trials could 'piggy back' onto infrastructure already in place for the late Phase II or Phase III trials in the general population. This would reduce start-up costs, separate monitoring requirements and increase the economies of scale. At the recruitment phase of the embedded trial, the enrollment of pregnant women might be enhanced, because the women do not perceive themselves as being singled out for research participation.

Furthermore, the embedded trial design would avoid the creation of a subgroup of pregnant women in selected populations to provide all of the safety data during pregnancy. With this design, both pregnant and nonpregnant participants would be drawn from the same population, thereby ensuring that the data generated could be generalized to the entire population. Once the clinical trial was completed, embedded trials involving pregnant women could provide pregnancy-specific data sooner than stand-alone trials because the subgroup analysis could be given priority. Additionally, it is possible that timely reporting of the subgroup analysis of research data from pregnant women would enhance the reporting of gender-specific analyses among nonpregnant research participants.

An important advantage of the embedded design would be the ability to directly compare safety and other outcomes in pregnant and nonpregnant women (and men), since these participants would be enrolled in the same trial and, therefore, would be directly comparable. It is likely that stand-alone Phase I trials in pregnancy would enroll only pregnant women because of the expense of including the nonpregnant controls. Therefore, comparison of data from pregnant women in stand-alone Phase I trials with

nonpregnant women and men in the initial Phase I or II trials would be equivalent to comparison with historical controls. By contrast, embedded Phase I trials in pregnant women would potentially increase the statistical power of the trial. If no differences were detected for a given outcome between pregnant and nonpregnant participants, then the data on these participants could be combined; this would increase the statistical power.

As with the option of stand-alone Phase I trials, however, there are limitations with the option of embedded Phase I trials. For a start, the logistics, procedures and record keeping with embedded trials would be more complicated than with stand-alone trials, as there would be different requirements for different participants depending upon whether they were pregnant and, for those who were pregnant, depending upon the stage of pregnancy. For example, assuring safety during the later stages of pregnancy, before enrolling pregnant women during the more vulnerable early stages of pregnancy, would be logistically more challenging.

Furthermore, identifying appropriate research sites might be more difficult with embedded trials, if otherwise ideal sites anticipated difficulties in recruiting pregnant women (owing to limited expertise with this participant population among the investigators at the site, limited access to this participant population and cultural norms precluding research involving pregnant women). This difficulty could be addressed by not requiring 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 nonpregnant 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 same time as Phase III trials in the general population and Phase I trials embedded into late Phase II or Phase III trials in the general population. Each of these options would be scientifically valid and meet the ethical imperative to include pregnant women in research. In the near future, however, we expect that stand-alone trials may well be preferred by researchers, research sponsors, research ethics committees and regulators, since these trials would be easier to monitor more closely and would not begin until Phase II trials in the general population were complete. As experience and expertise evolved, however, and the routine inclusion of pregnant women in clinical trials was more widely accepted, embedded trials could become the norm.

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, 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 nontreatment, undertreatment or mistreatment of pregnant women and their fetuses, and promoting fetal safety by reducing the number of pregnant women treated or vaccinated off-label.
- 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 into 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 nonpregnant 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 nonpregnant adults; (iii) reduced start-up costs and monitoring requirements; (iv) enhanced recruitment of pregnant women; (v) the ability to generalize research data to the entire population, as pregnant and nonpregnant participants would be drawn from the same population; (vi) the ability to provide pregnancy-specific data sooner than would be possible with stand-alone trials because the subgroup analysis could be given priority; (vii) enhanced reporting of gender-specific analyses among nonpregnant research participants and (viii) potentially increased 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.

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References

- 1 Levine R. *Ethics and Regulation of Clinical Research*, 2nd Edition. Baltimore: Urban Schwarzenberg, Baltimore, MD, USA (1986).
- 2 Emanuel E, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 283(20), 2701–2711 (2000).
- 3 Capron A. Legal considerations affecting clinical pharmacological studies in children. *Clin. Res.* 21, 141–150 (1973).
- 4 Baylis F, Downie J. An ethical and criminal law framework for research involving children in Canada. *Health Law J.* 1, 39–64 (1993).
- 5 Dresser R. Wanted: single, white male for medical research. *Hast. Cent. Rep.* 22(1), 24–29 (1992).
- 6 Baylis F. Women and health research: working for change. *J. Clin. Ethics* 7, 229–242 (1996).
- 7 Baylis F, Downie J, Sherwin S. Reframing research involving humans. In: *The Politics of Women's Health: Exploring Agency and Autonomy*. Sherwin S, Baylis F, Bell M *et al.* (Eds). Temple University Press, Philadelphia, PA, USA 234–259 (1998).
- 8 Lyerly AD, Little M, Faden R. The second wave: toward ethical inclusion of pregnant women in clinical research. *Int. J. Fem. Approaches Bioeth.* 1(2), 5–22 (2008).

- 9 Baylis F. Pregnant women deserve better. *Nature* 465, 689–690 (2010).
- 10 Baylis F, Kaposy C. Wanted: inclusive guidelines for research involving pregnant women. *J. Ob. Gyn. Can.* 32(5), 473–476 (2010).
- 11 Goldkind SF, Sahin L, Gallauresi B. Enrolling pregnant women in research – lessons from the H1N1 influenza pandemic. *N. Engl. J. Med.* 352, 2241–2243 (2010).
- 12 Macklin R. Enrolling pregnant women in biomedical research. *Lancet* 375(9715), 632–633 (2010).
- 13 Sackett DL, Rosenberg WMC, Gray JA, Haynes RB, Richardson WS. Evidence-based medicine: what it is and what it isn't. *BMJ* 312, 71–72 (1996).
- 14 Baylis F. Mandating research with children. *IRB: A Review of Human Subjects Research*. 21, 10–11 (1999).
- 15 Giacomini M, Baylis F. Excluding women from medical research: reasons and rejoinders. *Clin. Res.* 3, 12–15 (2003).
- 16 Rogers WA, Ballantyne AJ. Australian Gender Equity in Health Research Group. Exclusion of women from clinical research: myth or reality? *Mayo Clin. Proc.* 83(5), 536–542 (2008).
- 17 Adler NE. When separate is more equal. *JAMA* 304(24), 2738–2739 (2010).
- 18 Fisk NM, Atun R. Market failure and the poverty of new drugs in maternal health. *PLoS Med.* 5(1), e22 (2008).
- 19 Shanks N, Greek R, Greek J. Are animal models predictive for humans? *Philos. Ethics Hum. Med.* 4(2), e20 (2009).
- 20 Weetman AP. The immunology of pregnancy. *Thyroid* 9(7), 643–646 (1999).
- 21 Munoz-Suano A, Hamilton AB, Betz AG. Gimme shelter: the immune system during pregnancy. *Immunol. Rev.* 241(1), 20–38 (2011).
- 102 General Accounting Office. Testimony: NIH: Problems in implementing policy on women in study populations. (GAO/T-HRD-90–38) General Accounting Office, Washington DC, USA 1990. <http://161.203.16.4/d48t13/141601.pdf> (Accessed 31 October 2011)
- 103 US FDA Pregnancy categories. www.depts.washington.edu/druginfo/Formulary/Pregnancy.pdf (Accessed 31 October 2011)
- 104 US FDA. Proposed Rule. Content and format of labeling for human prescription drug and biological products; Requirements for pregnancy and lactation labeling. Federal Register 73(104), 30831–30868 (2008). www.gpo.gov/fdsys/pkg/FR-2008-2005-29/pdf/E8-11806.pdf (Accessed 31 October 2011)

Websites

- 101 Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, December 2010, Chapter 4. www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter4-chapitre4/ (Accessed 31 October 2011)