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THE INCLUSION OF PREGNANT WOMEN IN CLINICAL RESEARCH

BARBARA A. NOAH*

ABSTRACT: THE INCLUSION OF PREGNANT WOMEN IN CLINICAL RESEARCH

In the past three decades, there has been unprecedented growth in medical research utilizing human subjects, with much promise for new treatments that extend life, improve quality of life, and prevent disease and disability. Safe prescribing of drug therapies requires that researchers design clinical trials to test products for the benefit of all persons who are likely to utilize them, not just a limited population. For this reason, it is essential that clinical trials include women, pregnant women, children, and racial minorities, as appropriate, because these populations sometimes exhibit different patterns of response or adverse reactions.

Despite some significant progress in including women in clinical research, there is a dearth of sound research data on the safety and efficacy of already approved and commonly used medications for pregnant women. At this point, nearly all medications used to treat illness in pregnant women, including common chronic conditions such as hypertension, depression, diabetes, epilepsy, and cancer, are used off-label; that is, outside of the FDA-approved uses based on clinical trial and post-marketing data. Physicians must make prescribing decisions for their pregnant patients without the benefit of randomized, controlled clinical trials testing the safety and efficacy of drugs in pregnant women or the impact of these products on the health of the fetus. This problem of prescribing in the dark is receiving some attention in the medical and scientific community, but progress appears slow. Meanwhile, pregnant women face the difficult choice between taking untested drugs or foregoing necessary pharmacotherapy during pregnancy, potentially to the detriment of both woman and fetus.

The default position — to exclude pregnant women from clinical research — is untenable. Although serious challenges in study design, institutional review board (IRB) oversight, and research participant safety make the thought of research in pregnant women daunting, it is important to

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find ways to test commonly used drugs in pregnant patients. Postponing action until consensus on the ethical and regulatory issues can be achieved is no solution. Women get ill while pregnant or become pregnant while suffering from chronic illness, and therefore must sometimes take prescription and non-prescription medications. Researchers must, therefore, design and implement clinical trials and other types of data collection techniques for both new and already-approved drugs and therapies that will generate data for the safe use of these drugs for pregnant women and their fetuses. This article will describe the current status of inclusion of pregnant women in research, and will discuss some of the FDA-related regulatory barriers to collecting safety and efficacy information and approaches to improve the availability of data to support safe drug prescribing during pregnancy. Finally, although pro-life constituencies have significant influence on health policy, efforts to improve the quality and quantity of safety data should not bow to external, non-science-based attempts at interference with these goals.

I. INTRODUCTION

In the past three decades, there has been substantial growth in medical research utilizing human subjects, with much promise for new treatments that extend life, improve quality of life, and prevent disease and disability. Safe prescribing of drug therapies requires that researchers design clinical trials to test products for the benefit of all persons who are likely to utilize them, not just a limited population. For this reason, it is essential that clinical trials include all sub-populations who may utilize a particular drug. Although there has been good progress in the inclusion of women in clinical research,¹ the challenges of studying the safety of drugs in pregnant women has caused clinical research with this population to lag, leaving physicians and patients with inadequate data on which to base prescribing decisions. Various stakeholders have acknowledged the problem,² but progress appears slow.

For the past two decades, the government and the clinical research community have taken significant steps to include women, racial minorities, and children in clinical research in recognition of the fact that prescription drugs function differently and pose different risks among sub-populations.³ But it is only more recently that the question of how best to gather data on the safety of prescription drugs and other substances in pregnancy has

1. See Jesse A. Berlin & Susan S. Ellenberg, *Inclusion of Women in Clinical Trials*, 7 *BMC MED.* 56 (2009) (describing the variety of approaches used during the 1980s and 1990s to encourage equity for women in clinical research).

2. See, e.g., *NIH Looks to Increase Enrollment of Pregnant Women*, *GUIDE TO GOOD CLINICAL PRACTICE NEWSLETTER*, Feb. 1, 2011, available at <http://fda.complianceexpert.com/news/nih-looks-to-increase-enrollment-of-pregnant-women-1.93029?qr=1>; Mary A. Foulkes et al., *Clinical Research Enrolling Pregnant Women: A Workshop Summary*, 20 *J. WOMEN'S HEALTH* 1429, 1429 (2011).

3. The latest data demonstrate that women now make up the majority of clinical trial participants. In NIH-funded research, women now comprise over 63% of study participants. See OFFICE OF WOMEN'S HEALTH, FOOD & DRUG ADMIN., *DIALOGUES ON DIVERSIFYING CLINICAL TRIALS* 9 (2011), available at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM334959.pdf>. See also U.S. GOV'T ACCOUNTABILITY OFFICE, *GAO-01-754, WOMEN'S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT* (2001), available at <http://www.gao.gov/new.items/d01754.pdf>. Regulatory bodies have made similar efforts, with less success, to promote the inclusion of children and racial minorities in clinical research. See, e.g., Barbara A. Noah, *Just a Spoonful of Sugar: Drug Safety for Pediatric Populations*, 37 *J.L. MED. & ETHICS* 280, 280 (2009) [hereinafter Noah, *Spoonful of Sugar*]; Barbara A. Noah, *The Participation of Underrepresented Minorities in Clinical Research*, 29 *AM. J.L. & MED.* 221, 224 (2003) [hereinafter Noah, *Underrepresented Minorities*]. There is a related need for better training for physicians about sex-based differences in adverse drug reactions and sex-based recommendations for dosages. See *Editorial: Putting Gender on the Agenda*, 465 *NATURE* 665, 665 (2010).

received more direct attention; pregnant women are the last “orphaned” population in clinical research. The Second Wave Initiative, founded in 2009, is a collaborative organization of academics who are working to promote scientific and ethically sound research efforts in order to improve healthcare for pregnant women.⁴ The topic is also receiving much needed attention from other quarters, including the Office of Research on Women’s Health, part of the Department of Health and Human Services (HHS), which recently published proceedings from a research forum on the issues.⁵ The Institute of Medicine’s Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Research also has taken the position that pregnant women be “presumed eligible” to participate in clinical trials,⁶ a position that is very much the reverse of the current presumption against inclusion. All of this attention and action is significant but, unless the research community can address and overcome the predominant fear of injury to the fetus, progress will remain slow.

Pregnant women and their fetuses deserve healthcare, including prescription medications, that is based on sound scientific evidence of safety and efficacy.⁷ Women of childbearing age suffer from a number of common conditions that require prescription medication for treatment, yet do not preclude pregnancy.⁸ Women with chronic illnesses become pregnant, and pregnant women develop illnesses. The use of prescription drugs during pregnancy is therefore unavoidable, or at least medically appropriate at times. There is, however, a marked absence of sound research data on the safety and efficacy of most Food and Drug Administration (FDA) approved

4. THE SECOND WAVE INITIATIVE, <http://secondwaveinitiative.org> (last visited Apr. 16, 2014).

5. See NATIONAL INSTITUTES OF HEALTH OFFICE OF RESEARCH ON WOMEN’S HEALTH, INTRODUCTION TO ENROLLING PREGNANT WOMEN: ISSUES IN CLINICAL RESEARCH 7 (2010), available at <http://orwh.od.nih.gov/resources/policyreports/pdf/ORWH-EPW-Report-2010.pdf> [hereinafter ORWH REPORT].

6. WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES RELATING TO THE INCLUSION OF WOMEN IN CLINICAL RESEARCH 17 (Anna C. Mastroianni et al. eds., 1994).

7. See Laurence B. McCullough et al., *A Comprehensive Ethical Framework for Responsibly Designing and Conducting Pharmacologic Research that Involves Pregnant Women*, 193 AM. J. OBSTETRICS & GYNECOLOGY 901, 902 (2005) (discussing the use of psychopharmacologic drugs during pregnancy and noting that there is no objective evidence to guide prescribing of these drugs).

8. See Anne Drapkin Lyerly et al., *The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research*, 1 INT. J. FEMINIST APPROACHES TO BIOETHICS 5, 6 (noting that chronic diseases are common during pregnancy and include chronic hypertension, diabetes, psychiatric illness, cancer, autoimmune disease, and others, along with pregnancy-related conditions such as nausea and vomiting and preeclampsia).

and commonly used medications for pregnant women.⁹ The ethical issues that arise in designing sound scientific approaches to test drugs in pregnant women are complex and risk assessment is difficult, but procrastination is not going to make these challenges easier.

The physiological changes of pregnancy can affect how drugs are processed and excreted by the body, yet pharmacokinetic studies of approved drugs are rarely conducted in pregnant women.¹⁰ Pregnancy alters both liver and kidney function in ways that can significantly impact a drug's effectiveness.¹¹ At this point, nearly all medications used to treat illness in pregnant women, including common chronic conditions such as hypertension, depression, asthma, thyroid disease, diabetes, and epilepsy, are prescribed without adequate evidence about their safety for mother and fetus during pregnancy.¹² For prescription medications approved in the United States between 2000 and 2010, over 70% had no data on the risk of teratogenic harm,¹³ and 98% had insufficient data on which to assess this risk.¹⁴ Even for older drugs that have been on the market from 1980

9. There is a similar lack of data on the safety of drugs used in children and in preterm infants, though this topic is outside the scope of this paper. See, e.g., Jonathan M. Davis et al., *The Need for Rigorous Evidence of Medication Use in Preterm Infants: Is it Time for a Neonatal Rule?*, 308 JAMA 1435, 1435 (2012); Noah, *Spoonful of Sugar*, *supra* note 3, at 280 (describing a similar problem with safety and efficacy data for pediatric populations and recommending approaches to encourage clinical research with children).

10. See Sara F. Goldkind et al., *Enrolling Pregnant Women in Research – Lessons from the H1N1 Influenza Pandemic*, 362 NEW ENG. J. MED. 2241, 2241 (2010).

11. See *id.* at 2242. See also M.A. Andrew et al., *Amoxicillin Pharmacokinetics in Pregnant Women: Modeling and Simulation of Dosage Strategies*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 547, 547-56 (2007) (concluding that it may be impossible to provide doses of amoxicillin to pregnant women that will produce clinically effective drug levels in the blood because of altered renal function during pregnancy); Lyerly et al., *supra* note 8, at 8 (describing changes in blood flow through the kidneys that may result in higher metabolism of certain drugs and adding that changes in blood volume, sex hormones, and liver enzymes all can change how a pregnant woman's body processes drugs).

12. See Lyerly et al., *supra* note 8, at 7 (noting that only a dozen or so medications are expressly approved by the FDA for use in pregnancy and that they are all medications specifically related to pregnancy or childbirth related issues such as anesthesia, severe nausea and vomiting, and induction of labor).

13. A teratogen is defined as "an agent that can produce a permanent abnormality of structure or function in an organism exposed during embryonic or fetal life." See *Preamble, Teratogen Information System (TERIS)*, UNIVERSITY OF WASHINGTON, available at <http://depts.washington.edu/terisweb/teris/Preamble.htm> (last visited Apr. 16, 2014).

14. See Margaret P. Adam et al., *Evolving Knowledge of the Teratogenicity of Medications in Human Pregnancy*, 157 AM. J. MED. GENETICS PART C (SEMINARS MED. GENETICS) 175, 177 (2011) (reviewing the safety information available for the 172 drugs approved during this ten year period).

through 2000, it took an average of 27 years for sufficient data to be gathered on which to characterize the risk of teratogenicity.¹⁵

Physicians, therefore, often must make prescribing decisions for their pregnant patients without the benefit either of randomized, controlled clinical trials or retrospective observational studies evaluating the safety and efficacy of drugs in pregnant women or the impact of these products on the health of the fetus. This lack of clinical safety and efficacy data regarding prescription drugs for pregnant women creates a Catch-22 situation. In addition to the risk of injury to the fetus, prescribing drugs without adequate scientific evidence of safety and effectiveness in pregnancy risks inadequate treatment of the mother's medical condition and, of course, the mother's health may directly affect the health of the fetus. And, from an abundance of caution, some pregnant women may simply avoid taking medically necessary drugs during pregnancy, exposing themselves and the fetus to a different but equally serious kind of risk.

The lack of adequate safety information for drugs in pregnancy creates widespread risk because prescription and non-prescription drug use in pregnancy is common. The latest available data from the Centers for Disease Control and Prevention (CDC) show that nearly 90% of women take at least one medication during pregnancy and that 70% take at least one prescription medication.¹⁶ Moreover, in the past three decades, the use of prescription medications during the first trimester of pregnancy has increased by more than 60%.¹⁷ For example, data indicate that pregnant

15. See *id.* at 179 (evaluating the development of safety data on teratogenicity for drugs approved between 1980 and 2000 and concluding that, for the 5% of drugs that actually were assigned a pregnancy risk category, the "mean time for a treatment originally classified as having an undetermined risk to be assigned a more precise risk" was 27 years). See also W.Y. Lo & J.M. Friedman, *Teratogenicity of Recently Introduced Medications in Human Pregnancy*, 100 *OBSTETRICS & GYNECOLOGY* 465, 468 (2002) (concluding that, as of 2002, 91.2 % of drugs introduced to the market between 1980 and 2000 still had an undetermined risk of teratogenicity).

16. See *Data and Statistics: Use of Medication in Pregnancy*, CTRS. FOR DISEASE CONTROL, available at <http://www.cdc.gov/pregnancy/meds/data.html> (last visited Apr. 16, 2014) [hereinafter CDC Pregnancy Data]. See also Allen A. Mitchell et al., *Medication Use during Pregnancy with Particular Focus on Prescription Drugs: 1976 - 2008*, 205 *AM. J. OBSTETRICS & GYNECOLOGY* 51.e1, 51.e3 (2011) (analyzing data from more than 30,000 women and also finding that the use of four or more medications more than tripled and that prescription medication use was higher among more educated and older mothers and was highest among non-Hispanic whites); Susan E. Andrade et al., *Prescription Drug Use in Pregnancy*, 191 *AM. J. OBSTETRICS & GYNECOLOGY* 398, 400 (2004) (examining a prescription drug database and concluding that, as of 2004, approximately 64% of pregnant women in the U.S. receive prescriptions for one or more medications, not including prenatal vitamins).

17. See CDC Pregnancy Data, *supra* note 16.

women regularly receive prescriptions for antibiotics during pregnancy.¹⁸ Prescriptions for opioids and nonopioid analgesics for the management of pain during pregnancy have increased by 40% between 2001 and 2011.¹⁹ The use of over-the-counter medications is also common. Two studies that examined the medication histories of over 10,000 mothers found that at least 65% of women took acetaminophen during pregnancy, 18% took ibuprofen, and 15% took pseudoephedrine.²⁰ As for herbal supplements, nearly 11% of women report using herbal products three months before or during pregnancy.²¹

Antidepressant use during pregnancy has increased from 2.5% of pregnant women in 1998 to 8.1% in 2005.²² Many (but not all) women discontinue antidepressant use during pregnancy,²³ because there are indications of risk associated with these drugs for those who continue therapy throughout pregnancy. Although a large retrospective study of births in Nordic countries found no increased risk of stillbirth or infant mortality associated with the use of selective serotonin reuptake inhibitors (SSRIs), a

18. See Krista S. Crider et al., *Antibacterial Medication Use during Pregnancy and Risk of Birth Defects: National Birth Defects Prevention Study*, 163 ARCHIVES PEDIATRIC & ADOLESCENT MED. 978, 979-80 (2009) (concluding that several commonly-prescribed classes of antibiotics appeared safe for use in pregnancy and were not associated with increased prevalence of birth defects but recommending additional study of sulfonamides and nitrofurantoin, which are associated with increased birth defects including serious defects such as anencephaly and hypoplastic left heart syndrome).

19. See Antoine Malek & D.R. Mattison, *Drugs and Medicines in Pregnancy: the Placental Disposition of Opioids*, 12 CURRENT PHARMACEUTICAL BIOTECHNOLOGY 797, 797 (2011) (adding that women also self-medicate during pregnancy with previously prescribed opioids).

20. See Martha M. Werler et al., *Use of Over-the-Counter Medications During Pregnancy*, 193 AM. J. OBSTETRICS & GYNECOLOGY 771, 772 (2005) (concluding that “[s]tudies that examine specific over-the-counter medications in relation to specific birth defects are necessary to better inform pregnant women about risks and safety”).

21. See Cheryl S. Broussard et al., *Herbal Use before and during Pregnancy*, 202 AM. J. OBSTETRICS & GYNECOLOGY 443.e1-6, 443.e2 (2010) (recommending that physicians educate their pregnant patients about the use of herbal products during pregnancy and inform them that little is known of associated risks).

22. See Sura Alwan et al., *Patterns of Antidepressant Medication Use among Pregnant Women in a United States Population*, 51 J. CLINICAL PHARMACOLOGY 264, 265-66, 269 (2011) (examining the use of antidepressant medications in over 6500 mothers from ten states and recommending that healthcare providers “carefully assess and discuss the potential risks and benefits of continuing treatment during pregnancy with each patient”).

23. See I. Petersen et al., *Pregnancy as a Major Determinant for Discontinuation of Antidepressants: An Analysis of Data from the Health Improvement Network*, 72 J. CLINICAL PSYCHIATRY 979, 982 (2011) (finding that only 10% of women taking antidepressants before pregnancy were still taking the drugs at the start of the third trimester).

common form of antidepressant medication,²⁴ other studies indicate risk associations between SSRI use and congenital anomalies.²⁵ Another study found an increased risk of neonatal withdrawal²⁶ associated with the SSRI paroxetine.²⁷

A variety of factors appear to have contributed to the increased use of medication during pregnancy. In the 1960s, after the thalidomide tragedy, many pregnant women were reluctant to take any drug. Over time, however, the increasing availability of drugs for various conditions and the increased diagnosis of various medical conditions have led to more prescribing of drugs in general and during pregnancy.²⁸ Moreover, because half of pregnancies are unplanned,²⁹ and half of pregnancies go undetected until the fourth week after conception,³⁰ many women unknowingly take medications before realizing that they are pregnant.

The cause of most birth defects is unknown, though studies suggest that genetic factors such as chromosomal abnormalities and abnormalities of a single gene or gene pair account for about 25% of all congenital

24. See Olof Stephansson et al., *Selective Serotonin Reuptake Inhibitors during Pregnancy and Risk of Stillbirth and Infant Mortality*, 309 JAMA 48, 51 (2013) (finding a slightly higher rate of stillbirths and neonatal deaths in women who used SSRIs, but concluding that hospitalization for serious depression, smoking history, and advanced maternal age accounted for these differences, which were negligible once adjustments for these variables were taken into account).

25. See Carol Louik et al., *First-Trimester Use of Selective Serotonin Reuptake Inhibitors and the Risk of Birth Defects*, 356 NEW ENG. J. MED. 2675, 2675 (2007) (finding that SSRIs as a group posed no increased risk of anomalies, but concluding that certain drugs in the class were associated with a small but measurable increased risk of specific defects, although the overall increased risk was very small).

26. See Emilio J. Sanz et al., *Selective Serotonin Reuptake Inhibitors in Pregnant Women and Neonatal Withdrawal Syndrome: A Database Analysis*, 365 LANCET 482, 482 (2005) (explaining that neonatal withdrawal syndrome associated with SSRIs includes symptoms such as convulsions, irritability, abnormal crying, and tremor).

27. *Id.* at 484 (examining data from a large international database of adverse drug events and concluding that the data signals an increased risk: out of a total of 102 cases during the studied period from 11 different countries of SSRI use associated with either neonatal convulsions or withdrawal syndrome were identified, the drug paroxetine was the most commonly reported SSRI associated with these problems, although there were also cases associated with fluoxetine, sertraline, and citalopram).

28. See Jane E. Brody, *Too Many Pills in Pregnancy*, N.Y. TIMES, Feb. 25, 2013, available at <http://well.blogs.nytimes.com/2013/02/25/too-many-pills-in-pregnancy/> (providing the example of conditions like depression, which is now commonly diagnosed and treated with medication).

29. Stanley K. Henshaw, *Unintended Pregnancy in the United States*, 30 FAM. PLANNING PERSP. 24, 29 (1998).

30. R. Louise Floyd et al., *Alcohol Use Prior to Pregnancy Recognition*, 17 AM. J. PREVENTIVE. MED. 101, 101-07 (1999).

anomalies,³¹ while environmental factors including maternal infections and exposure to drugs or other chemical agents appear to cause approximately 10% of congenital abnormalities.³² The FDA estimates that less than 1% of birth defects are caused by medications taken during pregnancy, but notes that this estimate may be inaccurate because there is very little systematic effort to gather data on the question:

About 4 percent (1/28) of babies are born each year with a major birth defect or congenital malformation. The March of Dimes defines a major birth defect as an abnormality of structure, function, or metabolism that either is fatal or that is present at birth and results in physical or mental disability. For the majority of major birth defects (about 65 percent), the etiology is unknown. Chemically induced birth defects, including those associated with drug exposure, probably account for less than 1 percent of all birth defects; few drugs are proven human teratogens at clinical doses. Of the thousands of drugs available, only about 20 drugs or groups of drugs (most being anticonvulsants, antineoplastics, or retinoids) are recognized as having an increased risk of developmental abnormalities when used clinically in humans. However, since few drugs have been systematically studied to identify their full range of possible teratogenic risks, we cannot assume that current knowledge is complete. The identification of a drug's teratogenic potential is important because drug-induced adverse fetal effects are potentially preventable.³³

Although efforts to limit the impact of chromosomal and genetic abnormalities are beginning to succeed with the advent of more accurate and available prenatal testing, the impact of exposures to potentially teratogenic agents is also important because these exposures are often preventable.

The FDA's passive approach to collecting safety data on already-licensed drugs exacerbates the problem of inadequate drug safety data for pregnant women and fetuses. The FDA regulations require only that manufacturers of approved prescription drugs collect and forward to the agency adverse drug reaction reports (including reports of suspected harm to a pregnant woman or her fetus) through a voluntary system of adverse event reporting called MedWatch.³⁴ Although some data about adverse

31. See Robert L. Brent & David A. Beckman, *Environmental Teratogens*, 66 BULL. N.Y. ACAD. MED. 123, 125 tbl.1, 151(1990).

32. See *id.*

33. FOOD & DRUG ADMIN., REVIEWER GUIDANCE: EVALUATING THE RISKS OF DRUG EXPOSURE IN HUMAN PREGNANCIES 2 (2005), available at <http://www.fda.gov/downloads/sciencere search/specialtopics/womenshealthresearch/ucm133359.pdf>.

34. See Postmarketing Reporting of Adverse Drug Experience, 21 C.F.R. § 314.80 (2012).

events is better than none, the FDA's "mandatory" reporting system is only as effective as the extent of voluntary participation (through submission of adverse event reports by healthcare providers and patients to manufacturers) permits.³⁵ It often takes a good deal of time for sporadic reports of isolated adverse events to accumulate to the point that regulatory bodies or physicians can conclude that a particular drug poses risks to pregnant women or their fetuses.³⁶ A more active approach to data gathering for this population seems appropriate.

There are some systems currently in place to gather or assess safety data about drugs that are already in use in pregnant women. For example, the Teratogen Information System (TERIS) uses a process to attempt to quantify the risk of birth defects associated with various drugs and chemicals.³⁷ The information is compiled into a database that is available for physicians to consult, although the database is intended to guide decisions about whether to continue or terminate a pregnancy after exposure to a potentially teratogenic agent rather than as a guide for making prescribing decisions.³⁸ Although the availability of information to assess post-exposure risk in pregnant women is important, this information alone is insufficient to help physicians make prescribing decisions because the list of agents that have been assessed does not include all drugs prescribed to women of childbearing age. The CDC's Safer Medication Use in Pregnancy Initiative also seeks to collect and transmit data on medication use in pregnancy.³⁹

35. See Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare*, 49 CATH. U.L. REV. 449, 468-84 (2000) (describing and critiquing the FDA's MedWatch system).

36. FOOD & DRUG ADMIN., *supra* notes 33, at 3.

37. *Teratogen Information System and the On-line Version of Shepard's Catalog of Teratogenic Agents*, UNIVERSITY OF WASHINGTON, <http://depts.washington.edu/terisweb/teris/> (last visited Apr. 16, 2014).

38. See *id.* See also *Preamble, Teratogen Information System (TERIS)*, UNIVERSITY OF WASHINGTON, available at <http://depts.washington.edu/terisweb/teris/Preamble.htm> (last visited Apr. 16, 2014) (explaining that the analysis of various listed agents in the TERIS database "has been made on the basis of the reproducibility, consistency, and biological plausibility of available clinical, epidemiological, and experimental data. Reproducibility is judged by whether similar findings have been obtained in independent studies. Concordance is considered to be particularly important if the studies are of different design and if the types of anomalies observed in various studies are consistent. Effects seen in animal investigations are weighed more heavily if the exposure is similar in dosage and route to that encountered clinically and if the species tested are closely related to humans phylogenetically.").

39. See *Treating for Two: Safe Medication Use in Pregnancy Initiative*, CTRS. FOR DISEASE CONTROL, http://www.cdc.gov/ncbddd/birthdefects/documents/ncbddd_birth-defects_medicationuseonepager_cdcrole.pdf (describing the initiative activities including partnering with other federal agencies such as the FDA to gather data, developing a process for systematic, evidence-based review of medications used during pregnancy and "adverse fetal outcomes,"

There are also pregnancy registries for certain drugs that are known or suspected teratogens.⁴⁰

The lack of sufficient and reliable safety information about prescription and non-prescription drugs also has consequences for women who search for answers on the internet. As of 2006, 50% of women consulted the internet for health information,⁴¹ and that number has likely increased since then. Yet a recent study demonstrates that internet sources about drug safety during pregnancy contain substantial amounts of inaccurate and conflicting information.⁴² The investigators identified several deficiencies with the web sources, including lack of references from peer-reviewed literature, conflicting information about the safety of individual drugs, and some of the products listed as “safe” in fact are rated on TERIS as having a “none to minimal” or “minimal” risk or as having an “undetermined” risk of harm to the fetus.⁴³ Just over half of the websites suggested that women consult with a physician before stopping or beginning a medication during pregnancy, and less than 40% of the sites instructed women to take medications only when necessary.⁴⁴

The FDA is in the process of adopting revised drug labeling regulations to guide physicians in the prescribing of drugs for pregnant women. The original rule divided prescription drugs into five categories: A, B, C, D, and X to reflect different levels of knowledge about the pregnancy risks associated with various drugs.⁴⁵ These regulations require that all drugs (except for those which are not systemically absorbed) must contain information on the drug’s teratogenic and other effects on reproduction and pregnancy. This information must include, when available, a description of studies in humans with the drug and any available data on the drug’s effects on later growth and development of the child.⁴⁶ Pregnancy Category A

and publishing information related to medication use during pregnancy to educate healthcare providers and the public).

40. See *infra* notes 126-29 and accompanying text.

41. See Emily E. Petersen et al., *Prescription Medication Borrowing and Sharing among Women of Reproductive Age*, 17 J. WOMEN’S HEALTH 5 tbl.3 (2008).

42. Stacey L. Peters et al., *Safe Lists for Medications in Pregnancy: Inadequate Evidence Base and Inconsistent Guidance from Web-based Information, 2011*, 22 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 324, 325 (2013) (surveying 25 websites, including pregnancy information sites, 3 medical sites, and 17 clinical practice sources, that provided data about drug safety in pregnancy).

43. See *id.* at 325-26, 327 fig.1.

44. *Id.* at 325, 327 (arguing that these websites may provide false reassurance to women about the safety of various medications).

45. See Labeling Requirements for Prescription Drugs and/or Insulin, 21 C.F.R. § 201.57(c)(9) (2013).

46. See *id.*

refers to drugs for which adequate and well-controlled trials in pregnant women have demonstrated no risk to the fetus in the first trimester (and there is no evidence of risk later in the pregnancy).⁴⁷ Pregnancy Category B refers to drugs for which only animal studies have been conducted which demonstrate no risk to the fetus.⁴⁸ Category C applies to drugs for which animal studies show an adverse effect on the fetus, there are no adequate and well-controlled trials in humans, and the benefits of using the drug may outweigh its risks.⁴⁹ Category D includes those drugs for which there is positive evidence of risk to the human fetus based on adverse event reports or studies in humans, but the potential benefits of the drug may nevertheless outweigh the risks in some women.⁵⁰ Finally, Category X refers to drugs for which the evidence in animals or humans demonstrates a risk of fetal abnormalities and the risk of using the drug clearly outweighs any potential benefit.⁵¹ This category approach to pregnancy risk labeling has been roundly criticized because it fails to distinguish between the severity of various possible adverse outcomes associated with different drugs and it makes no distinction based on dose, route of administration, or timing of the use of the drug during the pregnancy.⁵²

The new proposed rule for pregnancy and lactation labeling which, as of early 2011, is in the final writing and clearance process,⁵³ alters this approach in several important ways. The proposed rule abandons the letter-based pregnancy categories in favor of a unified label format with three major components: a summary of risks, clinical considerations, and a data section.⁵⁴ The fetal risk summary begins with a one line conclusion that

47. 21 C.F.R. § 201.57(c)(9)(i)(A)(1) (2013).

48. 21 C.F.R. § 201.57(c)(9)(i)(A)(2) (2013).

49. 21 C.F.R. § 201.57(c)(9)(i)(A)(3) (2013).

50. See 21 C.F.R. § 201.57(c)(9)(i)(A)(4) (2013).

51. See 21 C.F.R. § 201.57(c)(9)(i)(A)(5) (2013).

52. See C.D. Chambers et al., *Drug Safety in Pregnant Women and their Babies: Ignorance Not Bliss*, 83 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 181, 182 (2008) (comparing two pregnancy category D drugs, one of which causes staining of the infant's teeth, while the other is associated with a high frequency of major birth defects, including spina bifida).

53. See *Pregnancy and Lactation Labeling*, FOOD & DRUG ADMIN. (Feb. 2, 2014, 11:46 AM), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>.

54. See *Summary of Proposed Rule on Pregnancy and Lactation Labeling*, FOOD & DRUG ADMIN. (Feb. 2, 2014 11:33 AM), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093310.htm>. See also *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, 73 Fed. Reg. 30831, 30838-39 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

describes the likelihood of four kinds of developmental abnormalities, including structural anomalies, fetal and infant mortality, impaired physiological function, and alterations to growth.⁵⁵ The clinical considerations section will cover three topics that physicians generally discuss with pregnant women and women of childbearing age, including inadvertent exposure to drugs early in pregnancy, prescribing decisions, and available safety data.⁵⁶ Although these changes to pregnancy labeling will help to avoid confusion, the FDA's requirements for providing information to prescribers is only as useful as the information available on which to base the risk assessment and clinical indications. Without better collection and distillation of that data, physicians will often still have to make prescribing decisions based on insufficient or entirely absent data.

This article will describe the current status of inclusion of pregnant women in research, and will examine the strengths and weaknesses of the current regulatory system for clinical trials with a view to identifying obstacles to increased data collection on drug safety in pregnancy. The article will then explore proposals to encourage the collection of rigorous evidence of safety for drugs used during pregnancy.

II. CLINICAL RESEARCH: REGULATORY BACKGROUND

The medical community often assumes over-optimistically that clinical research will yield additional scientific knowledge to the benefit of many patients.⁵⁷ In reality, the system of designing and regulating clinical research is highly flawed.⁵⁸ Although federal regulatory agencies and state health

55. See *Summary of Proposed Rule on Pregnancy and Lactation Labeling*, *supra* note 54 (adding that the risk summary must state whether the conclusions are based on human or animal data). See also 73 Fed. Reg. at 30840.

56. See *Summary of Proposed Rule on Pregnancy and Lactation Labeling*, *supra* note 54. See also 73 Fed. Reg. at 30843-44.

57. See Barbara A. Noah, *Bioethical Malpractice: Risk and Responsibility in Human Research*, 7 J. HEALTH CARE L. & POL'Y 175, 196-206 (2004) (describing pressures on the engine of biomedical research and inadequacies in the current system of clinical research oversight that may put participants at risk and that sometimes interferes with the quality of data); Roger N. Rosenberg, *Translating Biomedical Research to the Bedside*, 289 JAMA 1305, 1305 (2003) (questioning the "assumption that the recent exponential growth of scientific information about disease . . . heralds a rapid move to improve human health").

58. The United States Government Accountability Office (GAO) and the Department of Health and Human Services (HHS) have sounded the alarm, issuing highly critical reports about the ineffectiveness of IRBs. The HHS Office of the Inspector General (OIG) has issued a series of reports that criticize the operation of IRBs and Office of Human Research Protection's supervision of human research more generally. The reports focused on several problems endemic to IRB operations, such as overwhelming workload, lack of expertise, and conflicts of interest that interfered with proper review of research protocols. See, e.g., DEPT. OF HEALTH &

policy bodies have increased their scrutiny of research activities in recent years,⁵⁹ some risk to research participants is unavoidable.⁶⁰

A. *The Basics of Clinical Trial Regulation*⁶¹

Existing federal regulations delegate to IRBs the responsibility to safeguard research subjects who participate in clinical trials of experimental and approved therapies and in non-therapeutic trials designed to gain generalizable scientific knowledge. In order to protect human research subjects effectively, IRBs must use their combined expertise to assess the scientific, ethical, and legal validity of every proposed research protocol and must continue vigilant monitoring of ongoing approved protocols.⁶²

HUMAN SERVS., OEI-01-97-00193, INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM (1998); U.S. GOV'T ACCOUNTABILITY OFFICE, GAO/HEHS-96-72, SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS (1996). The Department followed up with another report that analyzed the extent of implementation of its recommendations. See DEPT. OF HEALTH & HUMAN SERVS., OEI-01-97-00197, PROTECTING HUMAN RESEARCH SUBJECTS: STATUS OF RECOMMENDATIONS (2000) (concluding that IRBs had made little progress in implementing the recommendations); U.S. GOV'T ACCOUNTABILITY OFFICE, HUMAN SUBJECTS RESEARCH, UNDERCOVER TESTS SHOW THE INSTITUTIONAL REVIEW BOARD SYSTEM IS VULNERABLE TO UNETHICAL MANIPULATION GAO-09-448T (2009) (identifying opportunities for fraud, manipulation, and deceit of institutional review boards by companies seeking clinical research approval).

59. See, e.g., Elisabeth Rosenthal, *New York Seeks to Tighten Rules on Medical Research*, N.Y. TIMES, Sept. 27, 1996, at B4 (describing the case of a 19-year-old healthy student volunteer at the University of Rochester who died during a study designed to measure the effects of pollutants on the lungs). HHS's Office for Human Research Protections (OHRP) temporarily suspended research under the supervision of IRBs at more than a dozen research institutions because of non-compliance with regulatory requirements. See Donald F. Phillips, *IRBs Search for Answers and Support during a Time of Institutional Change*, 283 JAMA 729, 729 (2000). OHRP also regularly criticizes the conduct of specified trials. See Robert Steinbrook, *Trial Design and Patient Safety – The Debate Continues*, 349 NEW ENG. J. MED. 629, 629 (2003).

60. HHS has issued an advance notice of proposed rulemaking requesting comment on how current clinical research regulations can be "modernized and revised to be more effective . . . [in protecting human subjects] . . . while facilitating valuable research and reducing burden, delay, and ambiguity for investigators." See Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44512 (proposed Jul. 26, 2011) (to be codified at 21 C.F.R. pts. 50, 56).

61. The regulatory description in this part is adapted from Barbara A. Noah, *Bioethical Malpractice: Risk and Responsibility in Human Research*, 7 J. HEALTH CARE L. & POL'Y 175, 182-96 (2004).

62. Much of this background section on clinical trial regulation is also adapted from Barbara A. Noah, *Bioethical Malpractice: Risk and Responsibility in Human Research*, 7 J. HEALTH CARE L. & POL'Y 175 (2004) (providing a more detailed discussion of IRB policies and practices).

There are two sets of parallel federal regulations applicable to human subjects research and these federal rules apply to most, though not all, clinical research conducted in the United States. The FDA regulations apply to all human subjects research involving products such as drugs, medical devices, and biological products that eventually will support a licensing application to the agency,⁶³ while the HHS regulations cover all research conducted or supported by the federal government.⁶⁴ These two overlapping sets of federal research regulations provide a wealth of detail about standards for approval and supervision of human research. Nevertheless, the regulations leave some of the most difficult scientific issues unresolved, and they leave important ethical questions to the discretion of IRBs, which may vary substantially in their interpretation and application of the regulatory requirements.⁶⁵

The regulations setting out criteria for approval require an IRB to assess a variety of scientific and ethical factors. First, the study design must minimize the risks to the subjects by using sound research procedures and, in the case of therapeutic research, by preferring procedures that typically would comprise standard diagnostic tests or treatment.⁶⁶ In addition to ensuring that risks to subjects are minimized, the IRB must evaluate whether those risks, whatever their magnitude, are reasonable in relation to the probable benefits to the subjects and the importance of the anticipated

63. See 21 C.F.R. § 50.1(a) (2013).

64. See 45 C.F.R. § 46.101(a) (2013). Many sections of the FDA and HHS regulations are nearly identical. For a useful comparison between the two sets of regulations, see *Comparison of FDA and HHS Human Subject Protection Regulations*, FOOD & DRUG ADMIN., <http://www.fda.gov/oc/gcp/comparison.html> (last updated Mar. 10, 2009). All institutions receiving HHS funding must provide the Department with assurances that every project conducted at the institution, regardless of the source of funding, will abide by the human subjects protection regulations. See 45 C.F.R. § 46.103(a) (2013).

65. Variations in IRB workload, institutional support and resources, and attitudes towards the informed consent process can lead to significant differences in the implementation of the federal regulations among boards, thereby potentially compromising this core mission. See JESSICA BERG ET AL., *INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE* 259 (2d ed. 2001); Jerry Goldman & Martin D. Katz, *Inconsistency and Institutional Review Boards*, 248 JAMA 197, 197, 198-99 (1982) (analyzing how 22 different IRBs reviewed identical research protocols, and reporting “substantial inconsistency” among boards in the application of both regulatory requirements for informed consent and ethical principles); Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 JAMA 360, 360, 364-65 (2003) (evaluating the review by 31 different IRBs of a multicenter cystic fibrosis genetic study, and concluding that the “highly variable” approaches of different boards compromised human subjects protection and created inefficiencies).

66. See 45 C.F.R. § 46.111(a)(1) (2013).

scientific knowledge.⁶⁷ Thus, the IRB must attempt to quantify and weigh potential risks and benefits to subjects associated with participation in the research.⁶⁸ This inquiry is necessarily complex and fact-intensive, and obviously more so in proposals to study the safety and efficacy of drugs in pregnant women because of the prospect of dual risk to both mother and fetus. In the case of therapeutic research, where the subjects suffer from the condition under investigation, there are both potential risks and direct benefits to participation. In non-therapeutic research, however, there is no prospect of direct benefit to the participants. In such cases, the IRB evaluates whether the possible benefit to society in the form of improved scientific understanding justifies the risks to individual research participants.⁶⁹ As explained within, virtually all research involving pregnant women must offer

67. See *id.* § 46.111(a)(2). IRBs do not, as a general matter, consider the ultimate cost of an experimental therapy, though perhaps they should. After all, if the experimental product will be very expensive compared with other available, efficacious therapies and thus will not constitute an important addition to the treatment arsenal for a particular condition, perhaps the benefits of the research may not justify its risks. Because the cost of some new therapies appears justified in patients who do not respond well to cheaper alternatives, however, and because IRBs have no crystal ball to determine which new therapies will fill such a niche, cost generally remains irrelevant to the IRB's assessment of the value of the potential scientific knowledge being sought. Compare Jean-Michel Gaspoz et al., *Cost Effectiveness of Aspirin, Clopidogrel, or Both for Secondary Prevention of Coronary Heart Disease*, 346 NEW ENG. J. MED. 1800, 1803-04 (2002) (concluding that the use of aspirin alone was the most cost-effective treatment for cardiac patients despite the fact that adding the more expensive drug clopidogrel increased therapeutic benefit), with Alastair J.J. Wood, *When Increased Therapeutic Benefit Comes at Increased Cost*, 346 NEW ENG. J. MED. 1819, 1820 (2002) (criticizing the study authors' recommendations, and arguing that the search for improved drug therapies should not be abandoned based on concerns about what they characterized as "unattractive" cost).

68. See 45 C.F.R. § 46.111(a)(2) (2013) ("In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)"). Not surprisingly, it is sometimes difficult for the subjects themselves to separate research-related treatments from standard therapies, especially if they are receiving both simultaneously and, therefore, difficult for prospective research subjects to weigh risk and benefit in deciding whether to participate. See *supra* notes 65-67, *infra* note 69 and accompanying text. Although the regulations only require IRBs to categorize risk for research involving children, see 45 C.F.R. § 46.404, it is common practice for IRBs to categorize risk in all research protocols. In the context of research on adults, the federal regulations only define "minimal risk." See *id.* § 46.102(i). Thus, IRBs must use their own judgment in determining what research activities constitute "greater than minimal risk." *Id.* § 46.404.

69. For example, Phase I clinical trials to assess the safety and appropriate dosing levels of an investigational new drug provide no direct benefit to the study subjects but represent a necessary step in the development of potentially useful drug therapies that ultimately may benefit large numbers of patients. An IRB may conclude that such research, if appropriately designed, meets the ethical standards implicit in the regulations.

the prospect of direct benefit to mother or fetus in order to satisfy ethical and regulatory requirements.⁷⁰

IRBs also must assess the scientific merit of each research proposal, a task that includes risk-benefit analysis but also considers the place of a particular research plan in the broader field of scientific inquiry. Research that lacks scientific merit is per se unethical and must not receive IRB approval. The assessment of scientific merit may prove difficult, however, even for a board of scientists and physicians. For example, if a protocol is designed to assess the safety and efficacy of a drug that will be the tenth in its therapeutic class and the study involves significant risk of side effects, the IRB may opt against approval. Similarly, IRBs may reject placebo-controlled studies that deny participants access to available standard therapy.⁷¹ In contrast, the IRB may more willingly tolerate a significant degree of risk to participants in a drug study involving a new molecular entity or other novel therapy intended to treat a serious or life-threatening condition for which available treatments are inadequate, even when the investigator provides only limited pre-clinical and clinical data about safety and effectiveness.⁷² In the case of research evaluating the safety and efficacy of prescription drugs in pregnant women, the IRB should consider as part of its risk-benefit calculus the frequency with which the drug is prescribed to this population, the severity of the condition that the drug is meant to treat and, of course, any known information about risk to the fetus.⁷³ All of these factors, taken together, provide some window into the scientific merit of the research plan, but without much data on which to base these evaluations, the IRB may be working in the dark.

The informed consent process is designed to reduce the knowledge gap between physician and patient by mandating the communication of

70. See *infra* notes 84-89 and accompanying text.

71. See, e.g., Ezekiel J. Emanuel & Franklin G. Miller, *The Ethics of Placebo-Controlled Trials – A Middle Ground*, 345 *NEW ENG. J. MED.* 915, 915 (2001) (arguing that “placebo-controlled trials are permissible when proven therapies exist, but only if certain ethical and methodologic criteria are met”); Benjamin Freedman et al., *Placebo Orthodoxy in Clinical Research II: Ethical, Legal, and Regulatory Myths*, 24 *J.L. MED. & ETHICS* 252 (1996) (challenging a number of common beliefs concerning the value of placebo controls); Sharona Hoffman, *The Use of Placebos in Clinical Trials: Responsible Research or Unethical Practice?*, 33 *CONN. L. REV.* 449, 475-95 (2001) (describing and discussing the competing arguments).

72. See Karen Antman et al., *Designing and Funding Clinical Trials of Novel Therapies*, 344 *NEW ENG. J. MED.* 762, 762 (2001) (observing that “[t]here are no clear criteria for determining when a procedure is optimally developed and when it is ready for randomized testing”).

73. See *infra* notes 84-89, 100-03 and accompanying text (discussing the regulations that specifically apply to research involving pregnant women and the challenges to IRBs and investigators in their implementation).

sufficient information to allow the patient to make meaningful decisions about healthcare.⁷⁴ It serves much the same purpose for potential clinical trial subjects and the researchers. Informed consent represents a necessary, though not sufficient, requirement for ethically appropriate research.⁷⁵ The regulations require that investigators obtain and document informed consent from each research subject,⁷⁶ but, of course, since the fetus cannot provide separate consent, the pregnant woman must make the decision whether to participate, taking into account the interests of the fetus. The consent form must use language that the subject can comprehend.⁷⁷ Both sets of regulations demand essentially identical elements in the disclosure of research procedures and risks to potential participants, including a description of the procedures to be followed, identification of any procedures which are experimental, a description of any reasonably foreseeable risks or discomforts to the subject, a description of any prospective benefits to the subject or to others, a discussion of alternative procedures or courses of treatment, if any, that might be advantageous to the subject, and a statement that participation is voluntary and that the

74. See Robert Gatter, *Informed Consent Law and the Forgotten Duty of Physician Inquiry*, 31 LOY. U. CHI. L.J. 557, 558 (2000); Joan H. Krause, *Reconceptualizing Informed Consent in an Era of Health Care Cost Containment*, 85 IOWA L. REV. 261, 267-78 (1999).

75. See Ezekiel J. Emanuel et al., *What Makes Clinical Research Ethical?*, 283 JAMA 2701, 2702-07 (2000) (discussing seven requirements, including informed consent, essential to the conduct of truly ethical research). See also Richard W. Garnett, *Why Informed Consent? Human Experimentation and the Ethics of Autonomy*, 36 CATH. U.L. REV. 455, 476-77 (1996) (explaining that informed consent in research pays "comparatively little attention" to whether the experiment itself is ethical).

76. See 45 C.F.R. § 46.111(a)(4)-(5) (2009).

77. See *id.* § 46.111. Despite the fact that many IRBs have interpreted the "language understandable to the subject" clause in this regulation to require informed consent forms to be written at an 8th grade reading level, IRBs have difficulty interpreting and enforcing this standard and comprehension problems remain. See Stanley Blenkinsop, *Whatever Happened to Plain English? The Gobbledygook Smokescreen that Baffles Research Subjects*, in VOLUNTEERS IN RESEARCH AND TESTING 76, 89-93 (Bryony Close et al. eds., 1997) (observing that "[t]here must be some suspicions that those unable to organise a clear, effective written explanation are equally unable to organise a clear, effective research programme," and providing some egregious examples of consent form "gobbledygook" with translations); Dale E. Hammerschmidt & Moira A. Keane, *Institutional Review Board (IRB) Review Lacks Impact on the Readability of Consent Forms for Research*, 304 AM. J. MED. SCI. 348, 349-50 (1992) (concluding that the IRB review process only improved consent form readability by an average of one-tenth of a grade level); Michael K. Paasche-Orlow et al., *Readability Standards for Informed-Consent Forms as Compared with Actual Readability*, 348 NEW ENG. J. MED. 721, 723-24 (2003) (providing examples of informed consent text at a variety of reading levels, and concluding that most medical schools did not comply with their own internal readability requirements).

subject may discontinue participation at any time without penalty.⁷⁸ Once the IRB approves the protocol and the consent form, the process of obtaining consent is left to the principal investigator or, more often, to his or her staff.⁷⁹ Unfortunately, the actual process of obtaining consent in research often emphasizes form over substance and thus falls short of promoting the ethical ideal of patient autonomy in making medical decisions.⁸⁰

IRBs suffer from significant limitations that impede their mission.⁸¹ Conscientious compliance with the minimal standards in the federal rules satisfies only a portion of the legal and ethical obligations in clinical research. Because the regulations only provide basic parameters for acceptable research, IRBs and investigators must exercise judgment in the interpretation and implementation of the rules. Understandably, caution prevails, both because of concerns about participant safety and potential liability should injury occur.

78. 45 C.F.R. § 46.116(a) (2009). In certain cases, the regulations require additional consent information, including statements about the risk to the fetus where the research involves pregnant women, circumstances under which the subject's participation may be terminated by the investigator, additional costs to the subject, and the number of subjects involved in the study. See § 46.116(b).

79. The IRB has the option of appointing a "consent monitor" to oversee this process. See § 46.109(e). IRBs rarely have the resources to exercise this authority.

80. See BERG ET AL., *supra* note 65, at 200. According to Franz Ingelfinger, "[t]he patient, asked to sign countless releases or consents, may respond with a . . . pro forma signature. The physician, immersed in a profusion of unimportant detail, will lose sight of, and respect for the important issues For medical ethics, in short, trivialization is self-defeating." *Id.* For a detailed discussion of these points, including a critique of the practice of obtaining consent in the research context, see Richard Delgado & Helen Leskovic, *Informed Consent in Human Experimentation: Bridging the Gap Between Ethical Thought and Current Practice*, 34 UCLA L. REV. 67, 75-80 (1986).

81. See Noah, *supra* note 57, at 196-206 (describing the changing climate of medical research – particularly pressures arising from increased research volume, the lack of effective training mechanisms, lack of expertise on IRBs in highly specialized fields of medicine, and complex relationships between academic researchers and private funding sources – increases the likelihood that these boards will fail in their mission to protect human subjects. In addition to failures to comply with explicit human subjects protection regulations, IRBs may underestimate risks, miss ethical or scientific deficiencies in the design of research protocols, or make other similar errors of judgment, thereby subjecting unwitting research participants to inappropriate and avoidable jeopardy. IRBs increasingly may face tort liability for "bioethical malpractice" — a failure to exercise reasonable judgment within the confines of the regulatory scheme governing human subjects research).

B. *Clinical Research Regulations Governing Research with Pregnant Women*

In recognition of past episodes of research abuse, the federal government also has promulgated regulatory protections providing additional safeguards to protect “vulnerable populations” in clinical research, including children, prisoners, pregnant women, the physically or mentally disabled, and educationally and economically disadvantaged individuals.⁸² The regulations pertaining to research involving pregnant women, human fetuses, and neonates set out requirements that IRBs and clinical investigators must meet in addition to the basic clinical research requirements in order to conduct research in this sub-population.⁸³ The regulations operate with a presumption of exclusion and only permit inclusion under very limited circumstances.

The current regulations require compliance with the following conditions in order for research involving pregnant women to be approvable: 1) if scientifically appropriate, preclinical studies, including animal studies and clinical studies on nonpregnant women, provide data to assist in risk assessment; 2) any risk to the fetus arises from interventions that also offer the prospect of direct benefit to the women or the fetus; or if there is no prospect of direct benefit, the risk to the fetus is no more than minimal and the research will likely assist in the development of important medical knowledge; 3) risks in the research are minimized as much as possible; 4) consent of the pregnant woman is required for research that offers the prospect of direct benefit to the pregnant woman and her fetus, the pregnant woman alone, or is minimal risk research with the prospect of obtaining important medical knowledge; 5) consent of the pregnant woman and the father is required for research that offers the prospect of direct benefit solely to the fetus (unless the father is unavailable, incapacitated, or the pregnancy has resulted from rape or incest); and 6) no monetary or

82. See 45 C.F.R. § 46.111(b) (2009). The federal research regulations do not, of course, reach research conducted in foreign countries, though other international standards on medical research such as the Nuremberg Code and the Declaration of Helsinki serve to protect foreign research subjects. Commentators strongly criticized overseas trials on maternal-fetal AIDS transmission using a placebo control because these trials violate basic international principles of human subjects protections. For more on the international dimensions of human subjects protections and vulnerable populations, see Jonathan Todres, *Can Research Subjects of Clinical Trials in Developing Countries Sue Physician-Investigators for Human Rights Violations?*, 16 N.Y.U L. SCH. J. HUM. RTS. 737 (2000); Harold Varmer & David Satcher, *Ethical Complexities of Conducting Research in Developing Countries*, 337 NEW ENG. J. MED. 1003 (1997).

83. See 45 C.F.R. § 46.203 (2009).

other inducements can be offered to the pregnant woman to terminate her pregnancy.⁸⁴

Several aspects of these regulations pose implementation or interpretive issues for IRBs. For example, the requirement that IRBs look for preclinical studies, including animal studies, for information to assist in risk assessment may create a de facto pattern of non-approval of research protocols that lack preclinical safety data.⁸⁵ Similarly, the question of whether proposed research creates a risk to the fetus that is “no more than minimal” leaves IRBs struggling to define the meaning of “minimal risk.”⁸⁶ More generally, quantifying risk and benefit in the context of proposed research with pregnant women is a very subjective process which is likely to vary considerably from one IRB to another.⁸⁷

By limiting research in pregnant women to those interventions (including prescription drugs) that either offer the prospect of direct benefit to the mother or fetus, or are otherwise posing no greater than minimal risk, the regulations take a very conservative stance on safety and have the effect of making some important research with pregnant women unapprovable. The regulations do include an exception for research that is not otherwise approvable, allowing HHS to conduct research that “presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, [and] fetuses,”⁸⁸ but the procedural requirements are onerous. The regulations require that the Secretary of HHS consult with an expert panel, publish a notice and opportunity for comment about the proposed research in the Federal Register, and must, based on comments and the deliberations of the expert panel, conclude either that the research does in fact satisfy the requirements above or that the research will be conducted according to sound ethical principles and appropriate consent will be obtained.⁸⁹ It is not difficult to imagine that various constituencies concerned with fetal life might register objections to clinical research involving pregnant women in these circumstances.

The presumption against inclusion of pregnant women in clinical research remains for now, but, at least as to research involving drugs that

84. See 45 C.F.R. § 46.204(a)-(e), (h) (2009).

85. See ORWH REPORT, *supra* note 5, at 39 (suggesting that “IRBs [may] wonder how much preclinical research is enough to ensure that there will be no harm to the fetus” and predicting that IRBs will be “conservative[]” in this assessment).

86. Cf. Foulkes et al., *supra* note 2, at 1431 (calling for “more regulatory clarity” with respect to what constitutes minimal risk to the fetus).

87. See ORWH REPORT, *supra* note 5, at 39.

88. See 45 C.F.R. § 46.207(a) (2013).

89. See 45 C.F.R. § 46.207(b)(1)-(2) (2013).

are regularly prescribed to pregnant women, the regulatory and research communities ought to consider the possibility of inclusion as a matter of routine, at least when the risk-benefit ratio appears favorable. The current regulations operate in exactly the opposite fashion, discouraging inclusion in a misguided attempt to avoid challenging ethical issues, possible injuries to research participants and fetuses, and potential liability. Of course these are genuine challenges, and it is impossible to eliminate them completely. At the same time, leaving pregnant women with the choice of foregoing medically necessary therapy or taking an untested drug and hoping for the best is clinically and ethically unacceptable.

III. SPECIAL CHALLENGES FOR RESEARCH WITH PREGNANT WOMEN

For both investigational new drugs and other types of biomedical research, the desire to streamline clinical trials in order to produce statistically significant results has led investigators to prefer homogenous patient populations for many types of studies. Until relatively recently, investigators almost uniformly tested new chemical entities only on white male subjects.⁹⁰ Although testing drugs in a homogenous white male population simplifies data collection and may generate clearer statistical differences between an investigational drug and an active or placebo control, this type of study design provides no information about the safety or effectiveness of the therapy in excluded sub-populations.⁹¹ Researchers also feared that women of childbearing age could become pregnant during research, and so routinely excluded women on this basis in order to avoid potential liability.⁹² In the past, commentators have devoted a good deal of attention to the inclusion of women in clinical trials.⁹³ Despite this attention

90. See Noah, *Underrepresented Minorities*, *supra* note 3, at 221 (discussing reasons for the exclusion of racial minorities including a history of distrust on the part of African American and other racial minorities of the medical research establishment and suggesting benefits of inclusion of these populations along with appropriate safeguards and considerations).

91. See Craig K. Svensson, *Representation of American Blacks in Clinical Trials of New Drugs*, 261 JAMA 263, 263-65 (1989).

92. See ORWH REPORT, *supra* note 5, at 7 (adding that this fear of liability was common despite a low number of research injuries and few lawsuits regarding such injuries).

93. See, e.g., Vanessa Merton, *The Exclusion of Pregnant, Pregnable, and Once-Pregnant People (a.k.a. Women) from Biomedical Research*, 19 AM. J.L. & MED. 369, 372 (1994); Joan W. Scott, *How Did the Male become the Normative Standard for Clinical Drug Trials?*, 48 FOOD & DRUG L.J. 187, 187-88 (1993) (describing two contradictory assumptions – that women are identical to men so that female participation in drug trials is unnecessary, and that women are so unlike men that female participation in drug trials would destroy the purity of the experiment – that have contributed to this phenomenon); L. Elizabeth Bowles, *The Disenfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap*, 45 VAND. L. REV. 877, 890 (1992).

to the issue in the literature, women still are underrepresented in many types of clinical trials.⁹⁴ The effect of gender imbalance in clinical research over time is “pernicious: medicine as it is currently applied to women is less evidence-based than that being applied to men.”⁹⁵

In 2001, the National Institutes of Health (NIH) published guidelines on the inclusion of women in research that state that “[i]t is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.”⁹⁶ Unfortunately, the NIH policy is silent on the matter of including pregnant women in research.

A. *Ethical Arguments for Inclusion of Pregnant Women in Research*

It is well-established that both the quantity and quality of safety data for prescription drugs in pregnancy is limited. The single most compelling argument for the inclusion of pregnant women in clinical research is that women, including those who are pregnant, deserve the same evidence-based medicine (in the form of safety data about prescription medications) that is available to others who take a prescription drug. As one commentator explains, “[t]o exclude any group or population from participating in medical research results in a lack of knowledge about the risks and potential benefits of products that will be available for their use once on the market.”⁹⁷ The usual procedure has been to remove a woman from a clinical trial if she becomes pregnant and then follow up to collect any information about adverse events, but the problem with this approach is that, for many drugs, harm may occur at different gestational periods, not only in the early stages of pregnancy.⁹⁸ Studying drug safety throughout

94. See Françoise Baylis, *Pregnant Women Deserve Better*, 465 NATURE 689, 689 (2010); Alison M. Kim et al., *Sex Bias in Trials and Treatment Must End*, 465 NATURE 688, 688 (2010).

95. Editorial, *Putting Gender on the Agenda*, 465 NATURE 665, 665 (2010) (adding that enrolling pregnant women in clinical research is fraught with ethical problems but that “ignoring the problem is not an answer either”).

96. See *Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October 2001*, NAT’L INSTS. OF HEALTH, http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm (last updated Oct. 1, 2001).

97. See Ruth Macklin, *The Art of Medicine: Enrolling Pregnant Women in Biomedical Research*, 375 LANCET 632, 632 (2010).

98. See *id.* at 633.

pregnancy will provide more data about risks associated with particular drugs.

In addition to the risk of harm to the mother or fetus from prescribing medication with an undetermined safety profile, there are other ethical arguments for inclusion of pregnant women. In the current climate in which physicians understand that there is a risk to the fetus with prescribing many unstudied medications, physicians may be hesitant to provide a pregnant woman with medically necessary treatment (for fear of injuring the fetus), therefore depriving her of potentially beneficial care. The failure to treat pregnant women for chronic or episodic illness can create riskier situations for the woman and/or her fetus than the use of an appropriate medication.⁹⁹

Although various governmental and private organizations have strongly encouraged the inclusion of pregnant women in research, there are problems with implementation of this still mainly aspirational goal. For example, the Council for International Organizations of Medical Sciences (CIOMS) published its *Guidelines for Biomedical Research Involving Human Subjects*, which states that pregnant women should be presumed eligible for biomedical research.¹⁰⁰ The commentary on this particular statement demonstrates some of the complexities that arise with implementation. If there is potential risk to the fetus and the research goals are directed towards the health of the fetus, the commentary suggests that the investigators should seek the father's opinion, when feasible, as well as the mother's consent.¹⁰¹ In addition to adding to the burden of conducting the research in general, it is reasonable to expect that, at least some of the time, seeking paternal assent will reveal a disagreement between the parents about the appropriateness of participation. What role then should the researcher play? And should the mother's consent trump the father's

99. See Lyerly et al., *supra* note 8, at 11-12 (discussing the risks of non-treatment or undertreatment of depression and asthma during pregnancy).

100. See, e.g., COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS 74 (2002), available at http://www.cioms.ch/publications/layout_guide2002.pdf. Guideline 17 states, "Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility. Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity."

101. See *id.*

disagreement? This requirement of paternal consent “when possible” is also inconsistent with the HHS regulations which mandate paternal (as well as maternal) consent for research that poses more than minimal risk but offers the prospect of benefit only to the fetus.¹⁰²

The CIOMS commentary also recognizes that, in some cultures or communities, the fetus’s health is considered more important than that of the mother and so suggests that “women may feel constrained to participate, or not to participate, in research” and that “[s]pecial safeguards should be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of direct benefit to the fetus.”¹⁰³ Again, it is important to recognize this point, but how should researchers or IRBs prevent inducement to pregnant women? These sorts of concerns, taken together with the natural ambivalence that many pregnant women will feel when considering research participation, are not easily answerable, but carefully considered and articulated standards for study design and inclusion can at least help to normalize participation and improve the consistency of IRB review and supervision of research protocols that include pregnant women.

B. *Recommendations for Ethically Appropriate Research Models*

The Randomized Controlled Trial (RCT) is still generally thought to be the gold standard of clinical investigation.¹⁰⁴ In general, new drugs and therapies undergo three phases of clinical testing after the completion of *in vitro* and animal studies. In the case of novel therapies, investigators may require several Phase II studies to evaluate technical feasibility questions, in addition to efficacy, before proceeding to Phase III trials that actually test the efficacy of investigational therapies in larger numbers of subjects who suffer

102. See *supra* note 84 and accompanying text.

103. See COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES, *supra* note 100, at 74.

104. See Ulrich Abel & Armin Koch, *The Role of Randomization in Clinical Studies: Myths and Beliefs*, 52 J. CLINICAL EPIDEMIOLOGY 487, 487 (1999); Stuart J. Pocock & Diana R. Elbourne, *Randomized Trials or Observational Tribulations*, 342 NEW ENG. J. MED. 1907, 1907 (2000) (advocating continued emphasis on RCTs, in part because in observational studies the treatment is selected for the particular patient and this selection bias may create cumulative outcome differences that are not a result of the treatment itself). *But see* Kjell Benson & Arthur J. Hartz, *A Comparison of Observational Studies and Randomized, Controlled Trials*, 342 NEW ENG. J. MED. 1878, 1883 (2000) (concluding that observational studies and RCTs were equally useful in accurately assessing the treatment effects of a wide variety of therapies); John Concato et al., *Randomized Controlled Trials, Observational Studies, and the Hierarchy of Research Designs*, 342 NEW ENG. J. MED. 1887, 1890 (2000).

from the targeted medical condition.¹⁰⁵ In contrast to RCTs, collecting data retrospectively from case reports or adverse event reports provides some information, but the low numbers of such reports usually means that the data are not statistically significant enough to conclude that a particular drug presents a particular risk in excess of the baseline risk.¹⁰⁶ Data from surveys can also lead to faulty conclusions when the response rate is poor, and uncontrolled studies that do not exclude confounding variables can also generate data of questionable validity.¹⁰⁷

Commentators have suggested that randomized clinical trials with pregnant women may be ethically acceptable under limited circumstances, specifically when they include careful assessment of scientific merit that concludes that a clinical trial of a particular drug is ethically justified under the circumstances. For example, such trials may be appropriate for drugs to treat conditions that affect pregnant women and for which there are no other acceptable treatments and for drugs that are designed specifically to treat pregnancy-related conditions.¹⁰⁸ Such studies might also be ethically appropriate in cases where pregnant women are already regularly taking a marketed drug and it has an established safety profile based on post-market reports.¹⁰⁹ Additional study in an RTC in such circumstances could confirm initial conclusions about safety, efficacy, and dosing or may also detect previously unknown risks. When RCTs do include pregnant women, it is important that the reviewing IRB consider risks and benefits to both mother and fetus holistically,¹¹⁰ not an easy task.

In the medical and ethics literature, commentators have suggested a number of strategies to minimize the risk of such research when it is conducted, including waiting to begin the research until there is sufficient pre-clinical data on which to assess toxicity, and monitoring the pregnancy

105. See LARS NOAH & BARBARA A. NOAH, *LAW, MEDICINE, AND MEDICAL TECHNOLOGY: CASES AND MATERIALS* 137-52 (2002) (discussing the various phases of drug development). In Phase I, a small number of healthy volunteers participate in a study to measure toxicity and to determine appropriate dosing. In Phase II, a somewhat larger number of individuals with the targeted disease or condition test the drug for efficacy and risks associated with its use. Finally, in Phase III, a large population of individuals with the targeted disease, along with a control group of some sort, test the product's safety and efficacy. See *id.* at 145-46.

106. See Christina D. Chambers et al., *Human Pregnancy Safety for Agents Used to Treat Rheumatoid Arthritis: Adequacy of Available Information and Strategies for Developing Post-Marketing Data*, 8 *ARTHRITIS RESEARCH & THERAPY* 225, 231 (2006).

107. See *id.* (adding that "information on outcomes is often incomplete without comprehensive data on the range of outcomes, including malformations, fetal growth and preterm delivery").

108. See Goldkind et al., *supra* note 10, at 2243.

109. See *id.* at 2242-43.

110. See Foulkes et al., *supra* note 2, at 1431.

via ultrasound and fetal heart monitoring in order to determine whether or when a particular subject should withdraw from the research.¹¹¹ The supervising IRB can also require that the trial be monitored by a Data Safety Monitoring Board (DSMB) in order to collect information about adverse events as the study is ongoing and respond quickly to evidence of toxicity, teratogenicity, or other problems.¹¹²

To state the obvious, the informed consent process with pregnant women in research must be thorough and meaningful. The consent process should include discussion of the known and potential risks of harm to the pregnant woman and her fetus and should afford the woman an opportunity to ask questions. This consent is always required in research, but, given the dual risk to the woman and her fetus, it deserves extra care in this context.¹¹³ At the same time, while informed consent is very important, viewing pregnant women as a “vulnerable” population seems, in some respects, inapt. While it may be true that the captive fetus is vulnerable to the results of the woman’s decision whether or not to participate in clinical research, it is surely not correct to suggest that pregnant women are somehow less able to provide valid informed consent to participation. Given the fact that regulations in the United States already require consent from the father under some circumstances, the combination of excessive paternalism and zero risk tolerance¹¹⁴ will continue to limit the opportunities for pregnant women to participate in research.

The federal regulations provide little guidance to investigators and research participants about how to evaluate risk in these circumstances. For this reason, a number of commentators have identified these gaps and

111. See Goldkind et al., *supra* note 10, at 2243 (adding that sufficient evidence of adverse effects might also require cessation of the entire clinical trial).

112. Some research protocols include a provision requiring ongoing supervision of approved research (between continuing reviews by the IRB) by an oversight committee such as a DSMB. IRBs have the authority to require DSMB oversight when they believe it to be appropriate. The NIH also requires that all NIH-funded trials have an appropriate oversight system, including DMBs for certain types of clinical trials. See Jay Herson, *Data Monitoring Boards in the Pharmaceutical Industry*, 12 STAT. MED. 555, 555-61 (1993) (describing the duties of these boards in different contexts such as NIH clinical trials and industry-sponsored trials); Michael A. Morse et al., *Monitoring and Ensuring Safety During Clinical Research*, 285 JAMA 1201, 1202 (2001) (describing the role of these boards in analyzing data from trials in progress).

113. See Macklin, *supra* note 97, at 633 (adding that IRBs will no doubt police consent carefully in this context but that “ultimately the responsibility falls to the investigators to ensure that all relevant information is presented and understood”).

114. See Lyerly et al., *supra* note 8, at 14 (explaining that “the need for thoughtful criteria has been eclipsed by a social tendency to regard the very idea of trading off risks between the woman and her fetus . . . however theoretical or small . . . as anathema”).

ambiguities in the federal research regulations and have offered specific analytical frameworks, consistent with the regulations, to guide IRBs and clinical investigators in filling those gaps. For example, one group of commentators has recommended a framework to evaluate risk and benefit to the mother and fetus, depending on the nature and goals of the research protocol.¹¹⁵ If the research is intended primarily to benefit the mother,¹¹⁶ this framework proposes that mothers of preivable fetuses retain the right to decide whether to confer dependent moral status on the fetus and thereby make decisions about research participation with beneficence towards the fetus in mind.¹¹⁷ For research that potentially affects viable fetuses, the framework suggests that “[t]he viable fetus is a patient in virtue of both its ability to survive ex utero and its access to medical technology that makes this possible”¹¹⁸ These commentators therefore suggest that, in the case of viable fetuses and preivable fetuses on whom the mother confers moral status, research for the benefit of the pregnant woman requires balancing maternal and fetal interests. The consent process in this context should ask the pregnant woman to balance her obligation to protect the fetus against her own health interests in participating in the research.¹¹⁹ This proposed framework, while consistent with the federal regulatory requirements, is not anywhere explicit in these regulations. Other commentators have commended these efforts but also offered critiques. In particular, these commentators have challenged the proposed framework as accepting without protest the presumption of exclusion and potentially posing yet another potential obstacle to the inclusion of pregnant women in research.¹²⁰

115. See McCullough et al., *supra* note 7, at 902-03.

116. By contrast, for research intended primarily to benefit the fetus, such as surgical treatment in utero of spina bifida, the study should be designed in such a way that pregnant subjects are exposed only to reasonable risks to their own health. See *id.* at 903.

117. See *id.* at 902 (explaining that “[t]he preivable fetus is a patient solely as a function of the pregnant woman’s autonomy”).

118. See *id.*

119. See *id.* at 903.

120. See Chris Kaposy & Françoise Baylis, *The Common Rule, Pregnant Women, and Research: No Need to “Rescue” that which should be Revised*, 11 AM. J. BIOETHICS 60, 60 (2011) (“At worst, the proposed framework could be another deterrent to such research by introducing additional barriers, and potentially ghettoizing research involving pregnant women.”); Anne Drapkin Lyerly et al., *Reframing the Framework: Toward Fair Inclusion of Pregnant Women as Participants in Research*, 11 AM. J. BIOETHICS 50, 50 (2011) (noting, among other criticisms, that the framework “appears to adopt a default position that current practice is necessarily safer or otherwise in the best interests of pregnant women or their fetuses than participation in research, despite the absence of evidence for the medical management of many medical conditions and risks experienced by pregnant women”).

The United States is not alone in its struggle to articulate the appropriate circumstances for the inclusion of pregnant women in RCTs and other sorts of research models that expose the woman or fetus to risk. The clinical research communities in other countries also struggle to describe those circumstances in which inclusion of pregnant women in clinical research are appropriate. Health Canada, for example, published a guidance document in 2012 which indicates conditions in which the inclusion of pregnant women in clinical research may be ethically acceptable.¹²¹ These conditions include the following:

- (i) The specific use of the therapeutic product is for pregnant or breastfeeding women (e.g. for obstetrical or pregnancy related problems).
- (ii) The studies are of agents which can be expected to address an unmet maternal /foetal risk or disease (e.g. pregnant women with HIV; other life threatening conditions) and where there are no alternatives available on the market.
- (iii) The studies are of agents which can be expected to improve maternal/foetal outcomes as compared to existing therapy.
- (iv) Animal studies have been conducted, including studies on pregnant animals, and there is data on non pregnant women on which to base an estimate of risk to the woman and/or foetus.
- (v) For a new drug or new indication there is anticipated or actual use of the drug in pregnant women and women of childbearing potential.
- (vi) The woman and/or foetus will benefit directly from participation and where any potential benefit to the foetus should be weighed against possible risks to the mother.
- (vii) The risk to the foetus is not greater than that from established procedures routinely used in an uncomplicated pregnancy, or in a pregnancy with complications comparable to those being studied, and the purpose of the research is the development of biomedical knowledge which cannot be obtained by any other means.
- (viii) The woman is fully informed of the risks to her, the foetus and the newborn . . .¹²²

In all of these circumstances, the emphasis is on balancing unknown risk against speculative prospective benefit. The prospect of direct benefit, as in cases where the study drug is anticipated to be used in pregnant women,

121. See HEALTH CANADA, HEALTH CANADA GUIDANCE DOCUMENT, CONSIDERATIONS FOR INCLUSION OF WOMEN IN CLINICAL TRIALS AND ANALYSIS OF DATA BY SEX (2012), available at http://www.elsevierbi.com/~media/Supporting%20Documents/The%20Gray%20Sheet/38/4/Canada_draft_guidance.pdf.

122. See *id.* at 14.

certainly would make participation more appealing for pregnant women with the targeted medical condition. Nevertheless, there is no way to “fully inform” the pregnant woman of the risks to her and the fetus; many of the risks remain a known unknown.

Other research models offer the potential for data collection without the ethical and regulatory complexity of RCTs. In addition to RCTs, another approach to collect safety and efficacy data involves performing carefully controlled pharmacokinetic studies (with sufficient numbers of pregnant women for adequate statistical power) in groups of pregnant women who are already taking the studied drug for therapeutic purposes.¹²³ It would also be useful to increase the prevalence of systematic observational studies of the effects of drugs on pregnant women and fetuses in order to obtain better quality data at a faster pace.¹²⁴ Since 2007, the FDA has authority to require Phase IV post-marketing trials as a condition of approval.¹²⁵ In such cases, the only added risk to the participating women and their fetuses would come from the blood draws required to measure how the body processes and excretes the drug. This approach represents a significant improvement over collecting and collating spontaneous reports of adverse events and offers the opportunity to detect adverse events more quickly and to improve information about optimal dosing.

Another route for collecting data, Pregnancy Exposure Registry Studies, involves enrolling pregnant women who are taking the drug in question for therapeutic purposes in a registry which collects information about outcomes.¹²⁶ Although more information is better than less, critics of the exposure registry approach to data collection point out that the outcomes information is usually limited to major birth defects, thereby excluding

123. See Goldkind et al., *supra* note 10, at 2243.

124. Cf. C.D. Chambers et al., *Drug Safety in Pregnant Women and their Babies: Ignorance Not Bliss*, 83 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 181, 181 (2008) (observing that, as of now, formal observational studies “are conducted in a piecemeal fashion for only a small fraction of available medications through the uncoordinated efforts of various individual investigators or state or federal agencies”).

125. See Food and Drug Administration Amendments Act of 2007 (FDAAA) § 901, 21 U.S.C. § 355(o) (2012) (authorizing the agency to require certain studies and clinical trials for prescription drugs and biological products approved under Section 505 of the Federal Food, Drug, and Cosmetic Act and requiring companies seeking marketing approval to provide to the FDA information about required postmarketing studies or clinical trials such as the timetable for completion and periodic status reports).

126. A list of pregnancy exposure registries may be found at *List of Pregnancy Exposure Registries*, FOOD & DRUG ADMIN., <http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm134848.htm> (last updated Mar. 6, 2014). For a discussion of the utility of pregnancy registries in the context of drugs for rheumatoid arthritis, see Chambers et al., *supra* note 106.

potential data about other adverse outcomes such as premature birth, developmental issues, and other potentially detrimental effects.¹²⁷ Nevertheless, a number of commentators have urged increased study of the safety of various classes of drugs during pregnancy, recommending organized retrospective data collection from pregnant women who must take prescription drugs in order to understand the impact of medications on the fetus.¹²⁸ The FDA also published guidelines on the design of pregnancy registries in order to address concerns about statistical power, more detail about timing and duration of exposure to the studied drug, and more detailed information about adverse outcomes, among other things.¹²⁹

There are already some programs in place to collect and disseminate information about pregnancy-related risks associated with certain drugs. The FDA, in collaboration with various pregnancy registries, collects data from pregnant women who take certain types of drugs in order to gather statistically significant data about the association of a particular drug with a birth defect. For example, the FDA recently released information about the risk of oral clefts (cleft lip or palate) associated with the use of the anti-seizure drug topiramate after the North American Antiepileptic Drug Pregnancy Registry found that the data suggested an increased risk to the fetuses of women taking this drug.¹³⁰ Based on the new data, the FDA recategorized the drug into pregnancy category D and advised women of childbearing age to discuss alternative treatments with their healthcare provider.¹³¹

The European Medicines Agency (EMA) also has published a Guideline that went into effect in 2006 and that recommends that manufacturers of new drugs to the market collect data via pharmacovigilance programs.¹³²

127. See Chambers et al., *supra* note 106, at 231-32.

128. See, e.g., Alwan et al., *supra* note 22, at 269; Chambers et al., *supra* note 124, at 182 (recommending a “national mandatory and systematic surveillance system for all newly marketed drugs used by women of childbearing age”); Putting Gender on the Agenda, 465 NATURE 665, 665 (2010) (recommending systematic retrospective data gathering from all women who have had to take prescription drugs during pregnancy).

129. See *Guidance for Industry: Establishing Pregnancy Exposure Registries*, FOOD & DRUG ADMIN. (Aug. 2002), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071639.pdf>.

130. See *Questions and Answers: Risk of Oral Clefts (Cleft Lip and/or Palate) in Infants Born to Mothers Taking Topamax (Topiramate)*, FOOD & DRUG ADMIN. (last updated Mar. 7, 2011), <http://www.fda.gov/Drugs/DrugSafety/ucm245470.htm>.

131. See *id.*

132. See European Medicines Agency, *Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data*, at 5-6, EMEA/CHMP/313666/2005 (Nov. 14, 2005), available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf.

The Guideline also recommends similar data collection for already marketed products in which safety during pregnancy is unknown.¹³³ The FDA and the EMEA share information from worldwide spontaneous reporting of adverse effects, and take appropriate action when necessary.¹³⁴ Collating spontaneous reports from multiple sources represents an improvement over prior practices, although the inherent deficiencies of spontaneous reporting remain.

The Organization of Teratology Information Specialists (OTIS) provides a website with detailed factsheets about the known risks of a variety of prescription and non-prescription drugs, herbal substances, and other common substances used during pregnancy (such as alcohol and caffeine) designed to educate mothers and prospective mothers about risks to the fetus.¹³⁵ In addition to providing risk information to expectant mothers, OTIS conducts and collaborates in research designed to compile new information about the risks of drugs during pregnancy. OTIS studies are designed to compare three groups of women with a particular medical condition requiring drug therapy. Group One includes women who have already taken a medication or vaccine and who have a health condition that is being studied. Group Two includes women who have the same health condition but who have not taken medication to treat it. Group Three serves as a control group and includes women who have neither taken the studied medication nor have the medical condition that the medication is designed to treat. By compiling comparative outcomes in pregnancy among all three groups, these studies aim to contribute information about risks to fetuses of various medications.¹³⁶

The OTIS study model includes several important features that make it superior to a traditional pregnancy registry, including the disease matched group which consists of women who have the disease in question and have

133. See *id.* at 5-6.

134. For example, the EMEA publishes a monthly report by its Pharmacovigilance Working Party that summarizes safety concerns associated with various types of drugs, including drugs taken during pregnancy. See, e.g., Pharmacovigilance Working Party July 2011 Plenary Meeting, July 18-20, 2011, *Monthly Report*, EMA/CHMP/PhVWP/569591/2011 (July 28, 2011) (describing the risk of side effects and withdrawal syndrome in newborns after exposure to antipsychotic drugs during the third trimester of pregnancy and recommending that product information in the EU contain additional information about this risk), available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109581.pdf.

135. See *Fact Sheets*, ORG. OF TERATOLOGY INFO. SPECIALISTS, <http://www.mohtertoba.org/otis-fact-sheets-s13037> (last visited Apr. 28, 2014).

136. See *Influenza Vaccine & Antiviral Medications Study*, ORG. OF TERATOLOGY INFO. SPECIALISTS, <http://www.mohtertobaby.org/otis-research-study-participation-p150175> (last visited Apr. 28, 2014).

not taken the studied drug or drugs. Having a disease matched control group allows for more accurate comparison of the rate of defects or other adverse effects in the group taking the drug than would be possible with a comparison of adverse effect rates in a broader background population. Moreover, the OTIS model requires the participating women to make a commitment to complete the study so that investigators typically get data from 95% of the women in any given drug study group. And, because the women remain in contact with the investigators throughout the course of the pregnancy and beyond, investigators are better able to collect information about potentially confounding variables such as non-prescription or herbal drug use, alcohol or tobacco intake, and other possible toxin exposures.¹³⁷

In addition to all of these benefits regarding the collection of more and better data, participation in studies such as those conducted by OTIS provides an "inclusion benefit" to the women in question. People in clinical trials also seem to enjoy generally better health outcomes compared with their peers who receive the same therapy outside of the study.¹³⁸ This "inclusion benefit," though unrelated to the specific clinical purposes of the study, represents a distinct and valuable bonus to those with limited access to healthcare services.¹³⁹

IV. CONCLUSION

The inclusion of pregnant women in clinical research deserves significant additional attention and effort for reasons of scientific equity and justice. All of the research models discussed above offer the prospect of increasing

137. See Chambers et al., *supra* note 124, at 232 (discussing the scientific superiority of the OTIS study design compared with traditional pregnancy registries and noting that participants get the added benefit of personal counseling about the risks of exposures to drugs during their pregnancies).

138. Commentators have recognized that subjects enrolled in clinical trials, whether they receive the experimental treatment or a placebo control, apparently achieve better outcomes than patients with the same condition who receive treatment from physicians. See John D. Lantos, *The "Inclusion Benefit" in Clinical Trials*, 134 J. PEDIATRICS 130, 130 (1999) ("A number of explanations have been offered for the apparent benefit of RCT participation, including selection bias, placebo effects, and adherence to well-defined protocols" for other aspects of disease management.); Shankar Vedantam, *Against Depression, A Sugar Pill is Hard to Beat*, WASH. POST, May 7, 2002, at A1. Of course, not all clinical research offers any prospect of a therapeutic benefit.

139. In one survey of potential research participants, 53% of those questioned indicated that they would be willing to participate in research in order to secure better medical care. See Vickie L. Shavers et al., *Factors that Influence African-Americans' Willingness to Participate in Medical Research Studies*, 91 CANCER 233, 235 (2001). See also Gina Kolata & Kurt Eichenwald, *For the Uninsured, Drug Trials are Health Care*, N.Y. TIMES, June 22, 1999, at A1.

access to safety and efficacy data in order to assist pregnant women and their physicians in making decisions about the risks and benefits to woman and fetus of prescription drugs at various stages of pregnancy. Although there seems to be a growing sense that this research is ethically necessary and appropriate, there does not (yet) appear to be much momentum to initiate this research, particularly randomized, controlled trials. Ultimately, the question is how we can move away from the presumed exclusion of pregnant women to a routine practice of inclusion when scientifically and ethically appropriate. This will require confronting valid fears of liability for injuries to mother or fetus¹⁴⁰ in a litigious society in which pro-life constituencies also have significant influence on health policy.

Serious challenges in study design, IRB oversight, and research participant safety make the thought of research in pregnant women daunting, but it is important to find ways to monitor and acquire data about the safety of commonly used drugs in pregnant patients. Pregnancy is a common condition, even among women who suffer from serious and chronic disease. Researchers must, therefore, design and conduct clinical trials for both new and already-approved drugs and therapies that will generate data for the safe use of these drugs. Phase IV trials involving careful monitoring of efficacy and adverse events in pregnant patients who receive approved drugs off-label will also contribute to the development of better data on which to base prescribing decisions. There is a growing consensus that RTCs are ethically appropriate under certain circumstances. Moreover, the OTIS model of research represents a substantial improvement over pregnancy registries and simple retrospective data collection.

It is no coincidence that pregnant women are the last “orphaned” clinical trial population in the United States. The research community in the United States is apparently reluctant to move forward with broader study of the effects of prescription drugs in pregnant women for several reasons. First, with the significant influence of the pro-life movement, it is likely that the government (in its regulatory and research funding roles) and clinical researchers are reluctant to risk the ire of political and religious conservative organizations. At the urging of pro-life groups, a number of state legislatures have considered “personhood” statutes that assign all of the rights and privileges of the state’s laws to fetuses at all stages of pregnancy.¹⁴¹ The Oklahoma Supreme Court recently struck down a ballot

140. See McCullough et al., *supra* note 7, at 903 (noting that clinical investigator concern about legal liability “surely counts as a legitimate self-interest”).

141. See Laura Guidry-Grimes & Elizabeth Victor, *Another Roadblock to Including Women in Research*, 42 HASTINGS CTR. REPORT 49 (2012) (discussing measures struck down in several states, including Colorado, South Dakota, California, and Mississippi).

initiative that would have ascribed all rights and privileges to fetuses at all stages of development because the law conflicts with U.S. Supreme Court decisions permitting abortion prior to viability.¹⁴² The problems with such laws include interference with legalized abortion, with the use of certain types of birth control, and potentially with a pregnant woman's participation in clinical research, if the research presented any potential for harm to the fetus.¹⁴³ The tragic situation of the recent Texas case in which a pregnant and brain dead woman was being maintained on "life support" in an effort to allow her fetus to develop sufficiently to be viable illustrates the lengths to which state legislatures will go in the name of protecting fetuses.¹⁴⁴ In a similar vein, the FDA in recent years has been influenced by the political interference of cultural and religious conservative groups in its evaluation of certain regulated drugs. As a recent example, last year, a federal court struck down the non-science-based compromise agreement to sell the so-called morning after pill, Plan B, over the counter for girls aged 15 and over who could present valid identification for proof of age.¹⁴⁵ In this type of regulatory culture, it is unsurprising that the relevant regulatory bodies, IRBs, and clinical researchers may hesitate to initiate research which may result in injury to a mother or her fetus, making the initiation of RTCs particularly difficult. IRBs and their members may also fear tort liability under these circumstances.

These concerns, together with the genuine challenges of informed consent, study design, and characterization of risk and benefit, make the prospect of clinical research with pregnant women quite daunting. In this culture, there remains a virtually zero risk tolerance for potential injury to the

142. See *In re Initiative Pet. No. 395*, 286 P.3d 637 (Okla. 2012) (finding that the measure violated *Planned Parenthood v. Casey*, 505 U.S. 833 (1992)).

143. See Guidry-Grimes & Victor, *supra* note 141, at 49 (suggesting that researchers in states with personhood legislation will be reluctant to enroll pregnant women and women of childbearing age for fear of liability).

144. See Nomaan Merchant, *Pregnant, Brain-Dead Woman's Husband Sues Hospital*, CHI. SUN-TIMES, Jan. 14, 2014, <http://www.suntimes.com/news/nation/24958547-418/pregnant-brain-dead-womans-husband-sues-hospital.html> (outlining the case of Marlise Munoz, discussing the Texas Advance Directives Act which states that, "A person may not withdraw or withhold life-sustaining treatment under this subchapter from a pregnant patient" and questioning this provision's applicability to a person who is legally dead).

145. See Brent Kendall & Mark H. Anderson, *Restricted Access to Plan B Pill Overturned*, WALL ST. J., Apr. 9, 2013, <http://online.wsj.com/news/articles/SB10001424127887324600704578404393383162004> (describing the opinion from Judge Edward Korman for the Eastern District of New York which concluded that the age restrictions for over the counter access to Plan B were "arbitrary and unreasonable"). See also *Tummino v. Hamburg*, 936 F. Supp. 2d 198 (E.D.N.Y. 2013) (discussing the political pressure brought to bear on the FDA and the Bush and Obama administrations with regard to the over-the-counter sales of Plan B).

fetus. Nevertheless, the need for more and better quality data about the safety and efficacy of prescription drugs for pregnant women and fetuses is sorely needed. We should not allow fear of liability or pressure from various political or religious groups to interfere with progress in clinical research that promises to improve the safety of prescription drugs for many pregnant women and their fetuses.

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