Published in final edited form as:

Curr Opin Psychiatry. 2009 November ; 22(6): 601–606. doi:10.1097/YCO.0b013e3283318e6f.

Ethical Issues in Perinatal Mental Health Research

Anna R. Brandon, Ph.D., M.S., Geetha Shivakumar, M.D., Simon Craddock Lee, Ph.D., MPH, Stephen J. Inrig, Ph.D., and John Z. Sadler, M.D.

The University of Texas Southwestern Medical Center at Dallas

Abstract

Purpose of Review—To review the background of current ethical standards for the conduct of perinatal mental health research and describe the ethical challenges in this research domain.

Recent Findings—Current literature reflects a growing sentiment in the scientific community that having no information regarding the impact of psychiatric treatment on the mother and developing fetus/infant poses dangers that may exceed the risks involved in research. However, without sufficient consensus across the scientific community, both regulatory bodies and perinatal researchers find themselves without a framework for decision making that satisfactorily limits the risks and facilitates the benefits of participation of pregnant and lactating women in clinical research.

Summary—Psychiatric research in perinatal mental health is critically important as it enables clinicians and patients to participate in informed decision-making concerning treatment for psychiatric disorders. Specific areas of concern include fetal safety, maternal risk, the therapeutic misconception, commercial interests, forensic/legal issues, the informed consent process, and study design. Developing guidelines that address ethical challenges and include the views and concerns of multiple stakeholders could improve the access of perinatal women to the benefits of participation in mental health research in addition to providing evidence-based mental health care for this subpopulation.

Keywords

pregnancy; bioethics; clinical research; human subjects

Introduction

Observers estimate over 500,000 women annually report a psychiatric condition predating or with onset during pregnancy, more than a third of whom take psychotropic medications during their pregnancy [1]. Clinicians typically consider medications to be first-line treatment for most psychiatric disorders, but concerns about randomizing pregnant or lactating women in pharmacotherapy trials prevent researchers from generating empirical data for pharmacological (and nonpharmacological) interventions during pregnancy. Presently, the US Food and Drug Administration (FDA) has approved less than a dozen medications for use during pregnancy, primarily preparations for nausea or anesthesia. The current regulatory climate discourages investigators from including ‘no treatment’ or wait-list control groups in perinatal studies, inhibiting thorough research of even low-risk non-pharmacological treatments. Clinicians and patients must make decisions based on observational and descriptive studies of pregnant women treated for psychiatric disorders or systematic data derived solely from non-pregnant samples.[2] However, as the knowledge of pharmacokinetics and

pharmacodynamics develops, it appears that pregnancy may confer unique biological differences in drug metabolism.[3] A growing consensus in the scientific community now considers this gap in information regarding the impact of psychiatric treatment on the mother and developing fetus/infant to pose dangers that surpass the risks involved in active research with this population.[4] Among the issues preventing pregnant women from receiving informed mental health treatment, foremost is that research and regulatory bodies lack established guidelines for evaluating the inclusion of pregnant women in drug studies. [2,4] Lacking scientific consensus on such inclusion, regulators and researchers are frequently forced to choose between accepting fetal risk and automatically excluding pregnant or lactating women. [5] Admittedly a complicated process, developing guidance for regulatory bodies must begin by identifying the primary liability concerns in perinatal research. A collaboratively designed framework built around these concerns would enable regulatory decision-making that manages the risks and benefits of participation, allowing suitable research to proceed. [2]

Legal and Regulatory History

Even though subject selection criteria for biomedical research have changed over time, developments in the USA during the latter decades of the twentieth century left women and minorities underrepresented in research. [6] Several controversial research cases between 1950 and 1974 prompted the American public to demand stricter research protections, particularly for vulnerable groups. [7] Policymakers implemented several reforms intended to safeguard subjects and spread research the burden of research more equitably, including the U.S. National Research Act (1974), the Belmont Report (1978), and the Common Rule (1981). [6,8]

Pregnant women figured prominently in these efforts. After thalidomide caused birth defects among European children, for example, the FDA toughened its drug safety and efficacy standards.[7] When faulty drugs and devices continued to harm women's offspring (i.e. diethylstilbestrol and the Dalkon Shield), the FDA in 1977 barred pregnant women and those of childbearing potential from early phase drug trials.[9]

In response, in the later 1980s, women's health advocates and AIDS activists demanded improved access for women into trials and increased funding for women's health concerns. [9] By 1993, advocates succeeded in convincing the FDA to reverse its "women of childbearing potential" policy and the NIH to devote millions of dollars to women's diseases. However, while women in general saw substantially increased access to clinical research thereafter, caution among researchers, funders, and regulators still kept most pregnant women from the process (for example, researchers had to meet ten criteria before they could enroll pregnant women in treatment protocols).[2,10]

Barring pregnant women from clinical trials has come with significant costs. Of the nearly 500 drugs approved in the US between 1980 and 2000, 2.5 percent held some known fetal risk, 6.4 percent qualified as little- or no-risk, and more than 91 percent remained 'undetermined' with respect to fetal risk.[11] Since most of these drugs address conditions not exclusive to pregnancy, when used during pregnancy those untested in specific perinatal populations are considered by some to be "off label," even when used appropriate to diagnosis.[2,12] Paradoxically, legitimate efforts to safeguard fetal health may have put both women and their fetuses at greater risk.

Current Guidelines

Although efforts have been made to eliminate paternalism and reduce the automatic exclusion of women with childbearing potential from research, [13] current guidelines remain vague and offer little direction in the management of risks and benefits of participation in research by pregnant women. Regulatory bodies, funding agencies, and perinatal mental health researchers

rely upon the Code of Federal Regulations produced by the Department of Health, Education, and Welfare, Title 45 Part 46 Subpart B (CFR), “Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research,” last revised in 2001 for guidance in decision making.[14] Although additional weight is given to reducing risks and the informed consent process, the additional protections surround (a) prohibiting researchers from having any part in the decision to continue or terminate pregnancy, and (b) including fathers in treatments of potential benefit or harm to the fetus (provided the father is available, assumed competent, and the pregnancy did not result from rape or incest). No specific DHHS regulations refer to research involving lactating women, however, the IRB Guidebook, produced by the Office for Human Research Protections (OHRP) of the DHHS, directs IRB reviews to focus on the safety of the nursing infant and requires investigators to provide assurance of safety to the child. [15] The Guidebook also enlarges upon the CFR with seven points of consideration for the review of studies involving perinatal women (see Figure 1). At the surface, these seven statements do not provide any rationale for automatic exclusion of pregnant or lactating women. However, suggestions are inherent in the statements that require information or special measures which may impede the inclusion of perinatal women in the trial. For example, words and phrases such as “appropriate,” “special monitoring,” “least possible,” “adequately informed,” “adequately protected,” and “adequately explained” provide a decision-making environment of subjectivity and encourage a general shrinking away from protocol approval.

Other guidelines referred to in the literature have been produced by the FDA and the American College of Obstetricians and Gynecologists (ACOG). [16-18] The FDA document, “General Considerations for the Clinical Evaluation of Drugs,” makes the general recommendation that women of childbearing potential should be excluded from all Phase I and II studies and included in further studies of investigational drugs only if “adequate information on efficacy and relative safety has been amassed.” The only cases in which such women could receive an investigational drug in the absence of adequate reproduction studies in animals are if the drug is being used as a life-saving or life-prolonging measure, where teratogenic potential has been established in animals, and in women in which the non-pregnant state is certain. The consenting process must include information concerning the lack of adequate animal research with the drug. ACOG guidelines are similar, but incorporate further encouragement to clarify the differences between appropriate health care and research objectives and include the father in the process of consent contingent upon the pregnant woman’s designation that he should be involved. As gate-keepers of access to research, IRBs and investigators alike are disadvantaged by the broad nature of these existing guidelines.

Our preliminary research investigating the ethical challenges of researchers in perinatal mental health has identified seven specific ethical areas that together account for the lack of consensus today between relevant stakeholders (identified as regulatory agencies, perinatal research investigators, community clinicians, perinatal women, research participants and their partners/fathers, funding agencies, pharmaceutical companies, and legal advisors) regarding the conduct of perinatal mental health research. We recognize other unidentified challenges may exist that future research might elucidate, however no literature to date has incorporated the values and beliefs of all these stakeholders. Though these seven areas are not exhaustive, they begin to address the ethical issues of perinatal mental health research.

1. Fetal safety

Fetal safety tops the list of reasons for excluding women from research, with most protocols stipulating that women of childbearing age adopt some form of contraception throughout the study duration. This concern may be somewhat misplaced; thalidomide, diethylstilbestrol (DES), and the Dalkon Shield caused tragedy for families because research into these products was ignored or inadequate, not because pregnant women participated in research trials. Simple

exclusion may not even protect women, for a cross-sectional study revealed that nearly half of all prenatal women reported the use of one or more medications during their pregnancy, the majority of which had an unknown FDA safety profile. [19] Additionally, approximately half of all pregnancies are unintended; women with unplanned pregnancies may have already exposed their baby to potential harm before even knowing they are pregnant. For women being treated for mental illness with psychotropic medications it can be even more complicated, because the side-effects of some psychotropic medications mirror the characteristics of early pregnancy (i.e. nausea, breast tenderness, amenorrhea), potentially delaying the detection of pregnancy.[20] With this multiplicity of unknown factors in play, we conclude that the reticence to include pregnant women in research trials leads to the alternately unacceptable risk of exposing millions of babies to compounds with unknown but potentially teratogenic fetal effects.

Meanwhile, observational research indicates that untreated maternal mental disorders do harm the fetus. Depression has been associated with fetal growth retardation, preterm birth, and longer stays in the NICU. [21] Babies born to mothers with schizophrenia have higher risks for preterm birth, low-birth weight, and post neonatal death than those born to normal mothers. [22] Serious maternal mental illness is also associated with smoking, substance and alcohol use, poor nutrition, and failure to access prenatal care—all of which adversely affect fetal/neonates.

As a result of debates over elective abortion, perhaps the greatest barrier to consensus regarding fetal safety is the oft-avoided question of the moral status of the fetus. [12] Does the fetus warrant equivalent moral respect compared to the mother? Ultimately what prevents pregnant women from general inclusion in research hangs upon the question of whether or not the fetus is a patient and could be harmed. Chervenak and McCullough propose that the fetus is a patient when two “links” exist between the fetus and its potential of achieving childhood and later personhood. [23] The first link is the viability of the fetus when mother presents for treatment or research, a function of biology and technology that presently occurs at approximately 24 weeks of estimated gestational age (EGA) as determined by ultrasound dating. The second link hinges upon the pregnant woman’s autonomy, her decision to continue a previable pregnancy to viability and later birth, either implicit (presenting for prenatal care) or explicit. Most discussions of perinatal research ethics tend not to consider this distinction between previability and viability, nor the pregnant woman’s right to confer (or deny) patient status on a previable fetus. Consequently, regulatory and funding agencies ultimately decide on fetal status when they deny participation in research to women who are pregnant or capable of becoming so in the study period.

2. Maternal Risks

Particularly in the previable fetus, total dependency on the maternal body makes investigating maternal and fetal risk as independent constructs artificial. Suicide, for example, is the ultimate maternal risk of untreated mental illness but almost always results in fetal death as well. While imprecise reporting makes estimates of pregnancy-related suicide are difficult, a recent review of the literature found suicide accounts for a significant proportion of pregnancy-associated death, and mental illness is always inferred to be the cause.[24] Discussions of the ethical challenges to perinatal research that focus solely upon the potential teratogenic risks to the fetus of maternal treatment ignore the equally intolerable risks generated by the unavailability of evidence-based treatment for mothers.

The risks of inappropriately treating mental illness are well established, but the psychological burdens of participating in research may be underappreciated for pregnant women. For example, faced with the odds of being randomized to a particular group in a given study, a non-pregnant woman may be quite able to live with the results of this decision post-participation.

Pregnant women, on the contrary, often feel responsible when things go wrong for their babies. Consequently, a pregnant participant may regret having accepted the risk of randomization in a trial at all, or wonder if her outcome would have been different if she had accepted treatment (or declined treatment) in a traditional clinical setting.[25] Ethical guidelines for perinatal research must consider all these facets of maternal health and well-being.

3. The Therapeutic Misconception

Broader structural conditions have ethical implications for perinatal mental health research, but they are insufficient to justify continuing to avoid perinatal research. A primary area of concern is the so-called “therapeutic misconception,” in which patients enroll in studies mistakenly expecting individualized treatment. [26] Within the current fragmented care delivery system, low-income and other vulnerable populations often look to mental health providers associated with academic medical centers and teaching hospitals to access mental health care. [27] Since these same institutions also conduct the bulk of psychiatric research, providers may face a conflict of professional interest and patients may blur the distinctions between treatment and clinical research. Indeed, community clinicians often assume that tertiary care centers provide better informed treatment and consequently refer perinatal women to these institutions, obfuscating the structured objectives of research to produce generalizable data. Similarly, efforts to distribute the burden of research and avoid the systematic exclusion of potential subjects from studies may themselves rest on a collective therapeutic misconception equating participation in clinical research as morally equivalent to universal access to standard of care treatment.[28] Importantly, evidence suggests that providers and clinical researchers themselves, not just patients and research subjects, can confuse the objectives of research with those of clinical care.[29] Clinics that serve the community in conjunction with conducting research must be aware that these two important goals are not uniformly co-terminus.

4. Commercial Interests

Industry concerns represent an additional impediment to perinatal research cited in the literature. Pharmaceutical companies have opted for a conservative industry model, foregoing perinatal research for fear of legal liability, increased costs, minimized profits, and recruitment difficulties. In view of the strict guidelines laid out in the FDA directive to industry, living in the present “off-label” environment is easier and more cost effective.[16] Surmounting this exclusionary culture in industry will require protections and incentives for research that are still ethically justifiable.

5. Forensic/legal issues

Daubert v. Merrell Dow Pharmaceutical established standards for the admissibility of scientific/technical evidence in civil lawsuits in the USA. [30] The *Daubert* ruling, a response to plaintiffs’ claims of birth defects due to a Merrell Dow product taken during pregnancy, now provides a technical standard for judges often adopted in considerations of admissibility of scientific or technical expert evidence. The criteria for scientific theory or technique to be admissible focused upon (1) empirical testability (falsifiability), (2) existence of relevant empirical science, (3) a reasonable rate of error, and (4) general acceptance of the theory/technique within the relevant scientific community. [31-33] The ruling poses a problematic paradox regarding clinical research in the perinatal setting: With substantive ethical constraints upon perinatal clinical research, the relevant evidence base to establish admissible evidence and establish expert witnesses under *Daubert* is never established. Therefore, real expertise does not exist to establish liability in “toxic tort” cases. [32] In effect, liability fears discourage the very studies that would diminish adverse sequelae of perinatal mental health treatment.

6. Informed Consent Document and Process

Two issues regarding the informed consent of perinatal women are highlighted in the literature, competency to consent and the inclusion of fathers. Community consensus already recognizes that psychiatric illness impairs independent, informed, and voluntary decision-making, but the question becomes even more salient in the perinatal research context: Can this mother fully consider the risks of this treatment to both her and her baby? [34,35] How can a researcher facilitate responsible decision-making? All guidelines stress the importance of providing adequate information regarding the availability of alternative care and the investigative goal of research, but it remains unclear how this process differs from the standard obligation researchers have to provide this information to any potential research participant. Equally unclear are statements about the inclusion of fathers when research poses risks or benefits to the fetus, because inclusion is contingent upon the father being available and competent, with no criteria given for establishing either.

7. Study Design

The randomized double-blind placebo controlled study (RCT) constitutes the “gold standard” in drug development, but researchers employ the placebo design component cautiously. According to the Declaration of Helsinki and the CFR, placebo-controlled trials are ethically acceptable only when 1) no current proven treatment exists, or 2) when comparing an existing treatment would somehow compromise the determination of safety and efficacy of the new treatment. [36] Moreover, choosing an appropriate control or comparison group in other studies depends upon whether any existing treatment meets “standard of care” guidelines in the management of a particular condition. Since treatments for psychiatric disorders occurring during pregnancy and lactation require *proof of efficacy* for mothers and *established safety* for fetuses, perinatal researchers find themselves in a paradoxical situation. They lack an evidence base from which to choose appropriate comparison groups, yet they cannot justify using a placebo in a comparison/control group owing to the paucity of knowledge about the impact upon the fetus. In view of the questions regarding potential differences in drug metabolism between pregnant and non-pregnant women, there is a strong need to study both efficacy and safety in this sub-population. However, our ethical guidelines remain insufficient to direct the implementation of the necessary RCT study design for such investigations. Consequently, the field is left with sub-optimal research from which we are unable to determine the best treatment for perinatal psychiatric disorders.

In any treatment trial, additional ethical issues regarding study design can occur during the actual implementation of a research protocol. For example, incidental findings may emerge that influence ongoing study participation, or a participant’s health may deteriorate, ushering in safety concerns. Standard protocols, such as leaving the participant in the study (and assigning worse rank) or treatment augmentation, may not be wise or may compound the risks to fetal safety in this sub-population. If we are to move forward in the field of perinatal mental health treatment, complex needs such as these must be addressed.

Conclusion

Perinatal women who suffer from psychiatric disorders, their families, and their clinicians urgently need treatment alternatives that have a basis for confidence in efficacy. Fetal safety, maternal risk, therapeutic misconception, commercial interests, forensic/legal issues, the process of informed consent, and study design all pose ethical challenges to conducting systematic research in mental health treatment of pregnant and lactating women. We require bioethical research to explore these and other potentially overlooked areas from the perspectives of multiple stakeholders in the treatment of this population. We join others in calling for guidelines, achieved by scientific consensus, that specifically address these issues.

They are essential if we are to advance our knowledge and provide women and babies the care necessary to protect maternal mental health without compromising fetal safety.

Acknowledgments

First author acknowledges support from Grant Number K23MH085007-02 (PI: Anna Brandon) from the National Institute of Mental Health (NIMH). Drs. Brandon, Shivakumar, Lee, and Sadler also acknowledge support in part from Grant Number UL1RR024982-03 (North and Central Texas Clinical and Translational Sciences Initiative; PI: Milton Packer) from the NIH National Center for Research Resources (NIH/NCRR).

References

- 1*. ACOG Practice Bulletin: Clinical guidelines for obstetrician-gynecologists number 92, April 2008. Use of psychiatric medications during pregnancy and lactation. *Obstetrics and Gynecology* 2008;111(4):1001–20. Unauthored. [PubMed: 18378767] This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists Committee on Practice Bulletins with the assistance of Zachary N. Stowe, MD and Kimberly Ragan, MSW and makes recommendations regarding the psychiatric treatment of perinatal women.
- 2**. Lysterly AD, Little MO, Faden RR. The second wave: Toward responsible inclusion of pregnant women in research. *The International Journal of Feminist Approaches to Bioethics* 2008;1(2):6–22. This thoughtful discussion reviews the history of the exclusion of women from research and presents the ethical responsibility to address the challenges of including pregnant women into research trials.
- 3*. Sit DK, Perel JM, Helsel JC, Wisner KL. Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. *J Clin Psychiatry* 2008;69(4):652–8. [PubMed: 18426260] This manuscript highlights the need to understand more about potential differences in drug metabolism during pregnancy.
4. Wisner KL, Appelbaum PS, Uhl K, Goldkind SF. Pharmacotherapy for depressed pregnant women: Overcoming obstacles to optimize treatment. *Clin Pharmacol Ther.* 2009 In Press.
- 5*. Rubinow DR. Antidepressant treatment during pregnancy: Between Scylla and Charybdis. *American Journal of Psychiatry* 2006;163(6):954–6. [PubMed: 16741191] Rubinow captures the dilemma clinicians and patients find themselves in when psychiatric disorders exist during pregnancy.
6. Epstein, S. *Inclusion: The Politics of Difference in Medical Research.* University of Chicago Press; Chicago: 2007.
7. Rice TW. The historical, ethical, and legal background of human-subjects research. *Respir Care Oct*; 2008 53(10):1325–9. [PubMed: 18811995]
8. Halpern, SA. *Lesser Harms: The Morality of Risk in Medical Research.* University of Chicago Press; Chicago: 2004.
9. McCarthy C. Historical background of clinical trials involving women and minorities. *Acad Med Sep*; 1994 69(9):695–8. [PubMed: 8074757]
10. Lysterly AD, Little MO, Faden RR. Pregnancy and clinical research. *Hastings Cent Rep Nov-Dec*;2008 38(6) Back cover.
- 11*. Lo WY, Friedman JM. Teratogenicity of recently introduced medications in human pregnancy. *Obstet Gynecol Sep*;2002 100(3):465–73. [PubMed: 12220765] This manuscript reviews what is known about teratogenic properties of current medications.
- 12*. Schwenzer KJ. Protecting vulnerable subjects in clinical research: children, pregnant women, prisoners, and employees. *Respir Care Oct*;2008 53(10):1342–9. [PubMed: 18811998] This is a systematic review of the protections for vulnerable populations.
- 13**. Goodrum LA, Hankins GDV, Jermain D, Chanaud CM. Conference Report: Complex Clinical, Legal, and Ethical Issues of Pregnant and Postpartum Women as Subjects in Clinical Trials. *Journal of Women's Health* 2003;12(9):857–67. This multidisciplinary group highlighted the legal, ethical, and financial issues that need better delineation and made nine consensus statements addressing the national problem of the underrepresentation of pregnant women in clinical trials.
- 14**. United States Department of Health and Human Services. Additional protections for pregnant women, human fetuses and neonates involved in research. Code of Federal Regulations. 2005 Title

45 Part 46 Subpart B. These are the existing guidelines for all research conducted or supported by the Department of Health and Human Services (DHHS).

- 15*. Penslar, RL. IRB Guidebook. U.S. Government Printing; Washington DC: This guidebook is published by the Office for Human Research Protections to aid IRB members and administrators focus on important areas of protection, providing information regarding existing consensus.
- 16*. Food and Drug Administration. General considerations for the clinical evaluation of drugs. U.S. Government Printing Office; Washington DC: 1977. Although under revision, these are the current guidelines for industry regarding pharmaceutical research.
- 17*. American College of Obstetricians & Gynecologists. ACOG Committee Opinion: Ethical considerations in research involving women. *Int J Gynaecol Obstet* Jul;2003 86(1):124–30. Number 290, November 2003. This publication provides current ACOG guidelines for perinatal research.
18. American College of Obstetricians & Gynecologists. ACOG Committee Opinion No. 377: Research involving women. *Obstet Gynecol* Sep;2007 110(3):731–6. [PubMed: 17766625]
- 19*. Lee E, Maneno MK, Smith L, Weiss SR, Zuckerman IH, Wutoh AK, et al. National patterns of medication use during pregnancy. *Pharmacoepidemiol Drug Saf* Aug;2006 15(8):537–45. [PubMed: 16700083] This publication reviews what is known about the use of medications by pregnant women.
20. Fitzgerald, P.; Seeman, M. Women and schizophrenia: Treatment implications. In: Castle, D.; McGrath, J.; Kulkarni, J., editors. *Women and Schizophrenia*. Cambridge University Press; Cambridge: 2000. p. 95-110.
21. Field T, Hernandez-Reif M, Diego M, Figueiredo B, Schanberg S, Kuhn C. Prenatal cortisol, prematurity and low birthweight. *Infant Behavior & Development* 2006;29(2):268–75. [PubMed: 17138282]
22. Hauck Y, Rock D, Jackiewicz T, Jablensky A. Healthy babies for mothers with serious mental illness: a case management framework for mental health clinicians. *Int J Ment Health Nurs* 2008;17(6):383–91. [PubMed: 19128285]
- 23*. Chervenak F, McCullough L. Ethical consideration of maternal participation in clinical research. *Curr Opin Obstet Gynecol* 1999;11(6):549–51. [PubMed: 10674830] These authors carefully discuss the moral status of the fetus and its impact upon perinatal research.
24. Shadigian E, Bauer ST. Pregnancy-associated death: a qualitative systematic review of homicide and suicide. *Obstet Gynecol Surv* Mar;2005 60(3):183–90. [PubMed: 16570396]
25. Hale B. Culpability and blame after pregnancy loss. *J Med Ethics* January 1;2007 33(1):24–7. 2007. [PubMed: 17209106]
26. Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: consent to research and the therapeutic misconception. *Hastings Cent Rep* Apr;1987 17(2):20–4. [PubMed: 3294743]
27. Cunningham PJ. Beyond Parity: Primary Care Physicians' Perspectives On Access To Mental Health Care. *Health Affairs* 2009;28(3):w490–w501. [PubMed: 19366722]
28. Capron AM. Ethical and human-rights issues in research on mental disorders that may affect decision-making capacity. *N Engl J Med* May 6;1999 340(18):1430–4. [PubMed: 10228198]
29. Joffe S, Weeks JC. Views of American oncologists about the purposes of clinical trials. *J Natl Cancer Inst* Dec 18;2002 94(24):1847–53. see comment. [PubMed: 12488478]
30. *Daubert v Merrell Dow Pharmaceuticals*. 1993.
31. Annas GJ. Scientific evidence in the courtroom--the death of the Frye rule. *Legal Issues in Medicine* 1994;330(14):1018–21.
32. Berger MA. What has a decade of Daubert wrought? *Am J Public Health* 2005;95(Supplement):S59–S65. [PubMed: 16030340]
33. Sadler, JZ. What can we ever know about the past? A philosophical consideration of the assessment of retrospective mental states. In: Simon, RI.; Shuman, DW., editors. *Retrospective Assessment of Mental States in Litigation: Predicting the Past*. American Psychiatric Press; Washington DC: 2002. p. 47-72.
34. Coverdale JH, McCullough LB, Chervenak FA, Bayer T, Weeks S. Clinical implications of respect for autonomy in the psychiatric treatment of pregnant patients with depression. *Psychiatric Services* 1997;48(2):209–12. [PubMed: 9021852]

35. Muroff JR, Hoerauf SL, Kim SY. Is psychiatric research stigmatized? An experimental survey of the public. *Schizophr Bull* Jan;2006 32(1):129–36. [PubMed: 16192411]
- 36**. Kupfer DJ, Frank E. Placebo in Clinical Trials for Depression: Complexity and Necessity. *Journal of the American Medical Association (JAMA)* 2002;287(14):1853–4. This publication addresses the role that placebo-controlled trials play in establishing evidence-based treatment.

1. For all studies, is there reason to exclude pregnant or lactating women? If so, how strict should the screening measures be?
2. For all studies involving pregnant women, have appropriate studies on animals and nonpregnant humans been conducted? Is any special monitoring of the informed consent process needed?
3. For studies directed toward maternal health, is the risk to the fetus the least possible consistent with the research objectives? Will the mother be adequately informed of the potential risk to the fetus and of alternative treatments and their risks and benefits?
4. For studies of pregnancy, labor, or delivery, is the risk to the fetus “minimal?” Is the father’s consent required?
5. For studies of lactating women, is the supply and content of breast milk adequately protected?
6. For studies of conception or contraception, are the risks, benefits, reversibility, and alternatives adequately explained? In contraceptive studies, is there adequate explanation of possible failure and of the options available for dealing with unintended pregnancies?
7. Will women be appropriately represented in the study? Does the study need to be designed to allow evaluation of gender differences?

Figure 1.
“Points to Consider” from the IRB Guidebook [15]