

## HIV, WOMEN, AND ACCESS TO CLINICAL TRIALS: TORT LIABILITY AND LESSONS FROM DES

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### I. INTRODUCTION

There is a growing recognition that disease processes, the manifestations of disease, and physiological responses to treatment sometimes may differ in men and women.<sup>1</sup> Thus, information from clinical studies that either exclude women or include them in numbers too small to provide meaningful information may be insufficient to extrapolate to health conditions and disease treatment in women.<sup>2</sup>

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1. For example, women develop coronary heart disease later than men, and manifest the disease differently, i.e., most men initially suffer a myocardial infarction while women have uncomplicated angina pectoris. See Jerry H. Gurwitz et al., *The Exclusion of the Elderly and Women from Clinical Trials in Acute Myocardial Infarction*, 268 JAMA 1417, 1421 (1992); Nanette K. Wenger et al., *Cardiovascular Health and Disease in Women*, 329 NEW ENG. J. MED. 247, 248 (1993). For other examples of gender differences that may be significant in the understanding of diseases and their treatment, see COMMITTEE ON THE ETHICAL AND LEGAL ISSUES RELATING TO THE INCLUSION OF WOMEN IN CLINICAL STUDIES, INSTITUTE OF MEDICINE, 1 WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 85-95 (Anna C. Mastroianni et al. eds., 1994) [hereinafter 1 WOMEN AND HEALTH RESEARCH] (identifying differences due to body size, composition, metabolism, aging, behavior, psychosocial responses, hormones, the use of exogenous hormones such as hormonal contraceptives and hormone replacement during menopause, and the physiological changes resulting from pregnancy and lactation); Ruth B. Merkatz et al., *Women in Clinical Trials of New Drugs: A Change in Food and Drug Administration Policy*, 329 NEW ENG. J. MED. 292, 292-93 (1993) (identifying sex-specific issues in drug response).

2. Until recently, women were under-represented in or excluded from research in numerous settings. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 49-67; Rebecca Dresser, *Wanted: Single, White Male for Medical Research*, HASTINGS CTR. REP., Jan.-Feb. 1992, at 24, 24-29 (examining white males as the prototype for medical research subjects). This failure to include women in study populations and its impact on women's health has been well documented in the areas of AIDS and cardiovascular disease. See, e.g., Ruth Faden et al., *Women as Vessels and Vectors: Lessons from the HIV Epidemic*, in FEMINISM & BIOETHICS: BEYOND REPRODUCTION 252, 253-70 (Susan M. Wolf ed. 1996) (discussing the health ramifications of excluding women from AIDS trials); Gurwitz et al., *supra* note 1, at 1421 (discussing the health ramifications of excluding women from cardiovascular disease trials); Wenger et al., *supra* note 1, at 248 (same).

Although many factors may have contributed to the underrepresentation of women in clinical studies,<sup>3</sup> the potential exposure of drug trial sponsors to tort liability frequently is cited as one of the primary reasons for excluding women from trials.<sup>4</sup> The true source of legal anxiety in the recruitment of female research subjects arises, however, not from a concern for women's safety, but from the fear of potential injuries to their offspring.<sup>5</sup> Observations and reports of birth defects in children of women who had been treated with thalidomide or bendec-

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3. Some factors that may have influenced decisions to exclude women from research projects are insensitivity to women's health issues, lack of representation of women on decisionmaking bodies, gender bias, reliance on the male norm in study design, failure to recognize diversity among the population of women, and perceived difficulties in recruitment and retention of women subjects. See generally 2 WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES, WORKSHOP AND COMMISSIONED PAPERS (Anna C. Mastroianni et al. eds., 1994) [hereinafter 2 WOMEN AND HEALTH RESEARCH]. Earlier federal regulations also contained restrictions on women's participation in research projects. See FDA Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, 58 Fed. Reg. 39,406, 39,408 (1993) ("[An earlier FDA guideline] has restricted the early accumulation of information about response to drugs in women that could be utilized in designing phase 2 and 3 trials, and has perhaps delayed appreciation of gender-related variation in drug effects. This early exclusion also may have perpetuated, in a subtle way, a view of the male as the primary focus of medicine and drug development, with women considered secondarily"); see also Nancy E. Kass et al., *Harms of Excluding Pregnant Women from Clinical Research: The Case of HIV-infected Pregnant Women*, 24 J.L. MED. & ETHICS 36, 38-39 (1996) (discussing federal oversight of research involving pregnant women); Vanessa Merton, *The Exclusion of Pregnant, Pregnable, and Once-Pregnant People (a.k.a. Women) from Biomedical Research*, 19 AM. J.L. & MED. 369, 390-400 (1993) (discussing federal regulatory constraints on including women in research). This Article will not explore the potential for male mediated developmental toxicity in offspring, as that has not, to the author's knowledge, proven to be a barrier to men's access to clinical trials.

4. See, e.g., Ellen Flannery & Sanford N. Greenberg, *Liability Exposure for Exclusion and Inclusion of Women as Subjects in Clinical Studies*, in 2 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 91-102; Merton, *supra* note 3, at 400.

5. See Ellen Wright Clayton, *Liability Exposure When Offspring Are Injured Because of Their Parents' Participation in Clinical Trials*, in 2 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 103, 106-07; Flannery & Greenberg, *supra* note 4, at 94-96; 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 159-65; R. Alta Charo, *Protecting Us to Death: Women, Pregnancy, and Clinical Research Trials*, 38 ST. LOUIS U. L.J. 135, 139-40, 144-46 (1993); Kass et al., *supra* note 3, at 36-46; Merton, *supra* note 3, at 400; Karen H. Rothenberg, *Gender Matters: Implications for Clinical Research and Women's Health Care*, 32 HOUS. L. REV. 1201, 1259-63 (1996).

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tin brought liability concerns to the forefront.<sup>6</sup> When the courts held manufacturers liable for injuries caused to the offspring of women exposed to Diethylstilbestrol (DES), it became yet another reason for excluding pregnant women and women of childbearing age from clinical trials.<sup>7</sup>

The failure to include adequate numbers of women in clinical studies of HIV and AIDS has had a significant impact on the health and welfare of women afflicted with the disease.<sup>8</sup> In addition, proponents of the inclusion of women claim that women's underrepresentation endangers not only the health of each individual woman denied the opportunity to participate, but also jeopardizes the

6. See Joseph Sanders, *The Bendectin Litigation: A Case Study in the Life Cycle of Mass Torts*, 43 HASTINGS L.J. 301, 313-21 (1992) (describing drugs, their uses, and effects). Thalidomide was prescribed as a sedative in Europe during the late 1950s and early 1960s. See *id.* at 313. The children of pregnant women who were given the drug frequently suffered severe birth defects, including "arm and leg deformities." *Id.* FDA approval to market thalidomide for use in the United States ultimately was withheld because of these and other reports of harmful effects in humans. Recently, however, alternative uses of thalidomide are being considered. See *FDA Moves on Thalidomide*, 350 LANCET 1086 (1997). Bendectin was used as an anti-nausea drug for pregnant women from the mid 1950s through the 1970s. See Sanders, *supra*, at 317. Despite a 1980 report by the FDA's Fertility and Maternal Health Drug Advisory Committee that the drug had no teratogenic effects, it was blamed for a wide variety of birth defects, including "limb reductions." *Id.* at 318. In response to multiple product liability suits, the manufacturer, Merrell Dow, withdrew the drug from the market in 1983; because most states have lengthy statutes of limitations regarding childhood disability, the company continues to fight legal actions today. See *id.* at 319-20. Merrell Dow recently reported that only one verdict against the company remains and it is on appeal on the grounds that the scientific evidence does not support the verdict. See *Merrell Dow Wins Reversal in Texas Bendectin Case*, NAT'L L.J., Aug. 18, 1997, at A12. Neither of these drugs resulted in reported research injury cases.

7. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 40 ("[P]roblems caused by . . . diethylstilbestrol (DES) . . . would amplify public sentiment about the need for greater protection for fetuses . . .").

8. Existing data indicate that women's participation in AIDS clinical drug trials has been low. See 62 Fed. Reg. 49,946, 49,947 n.1 (1997) (to be codified at 21 C.F.R. pt. 312) ("As of January 1992, 14,799 participants were enrolled in U.S. AIDS Clinical Trial Group studies sponsored by the National Institute of Allergy and Infectious Diseases, of whom only 1,151 were adult women. In 1993, 21,598 participants were enrolled, while only 1,952 were adult women." (citations omitted)); Faden et al., *supra* note 2, at 252-53 (noting that until recently the research examining HIV and AIDS in women focused on women's potential to infect others "either as sexual partners . . . or as gestators" and that "[t]he health interests of women themselves largely were ignored . . . result[ing] in harm to women."). Furthermore,

[t]he delay in examining how AIDS manifests itself in women has resulted in women's conditions being conspicuously absent from the list of conditions defined by the Centers for Disease Control and Prevention (CDC) to constitute AIDS, and this in turn has resulted in the denial of benefit and treatment programs to women. . . . [I]n clinical trials of AIDS drugs, which often may provide significant sources of first-rate medical care and access to experimental treatment for persons with AIDS, the numbers of women participating lags behind expectations for a disease that is increasing the most rapidly among women.

. . . [W]here women have been the focus of clinical research the primary research question has been how to reduce or prevent a vertical transmission of [HIV] from a pregnant woman to a fetus or newborn, not how to treat the female-specific manifestations of HIV diseases. . . . [U]ntil very recently there has been almost no research explaining the mechanisms of male-to-female transmission of HIV and little research directed at the development of anti-viricidal [sic] preparations that could be used by women to reduce their chances of contracting the infection through sexual activity.

1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 66; see generally GENA COREA, *THE INVISIBLE EPIDEMIC: THE STORY OF WOMEN AND AIDS* (1992) (discussing how excluding women from clinical studies results in little available information on how HIV affects women).

health of their potential offspring.<sup>9</sup> In light of the growing number of AIDS cases in women between the ages of twenty-five and forty-four,<sup>10</sup> it is critical that the health needs of this subgroup, which encompasses women of childbearing age and pregnant women, be addressed and that this population not be denied the benefits of research.<sup>11</sup>

Recently, pregnant women have served as subjects in clinical trials of AZT.<sup>12</sup> The federal government, stimulated by the AIDS crisis in women, has introduced guidelines and proposals to encourage the inclusion of women of child-

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9. See Nancy Kass, *Gender and Research*, in *BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH* (Jeffrey Kahn et al. eds., forthcoming 1998) (noting that work in maternal epilepsy, asthma, diabetes, and HIV all demonstrate that a fetus that develops in a maternal environment that is relatively healthy has a much better outcome and prognosis than a fetus that develops in the context of uncontrolled maternal disease); see also JACK A. PRITCHARD ET AL., *WILLIAM'S OBSTETRICS* 257 (18th ed. 1989) (noting that good prenatal care benefits both the baby and mother); Kass et al., *supra* note 3, at 37 (discussing the inclusion of HIV-positive women in clinical research); Merton, *supra* note 3, at 377-79 (discussing the immediate benefits from research that women do not get because they are excluded); Rothenberg, *supra* note 5, at 1208-09 (discussing gender gaps in clinical research).

10. See Centers for Disease Control & Prevention, U.S. Dep't of Health & Human Servs., *Update: Mortality Attributable to HIV Infection Among Persons Aged 25-44 Years—United States, 1994*, 45 *MORBIDITY & MORTALITY WKLY. REP.* 121, 123 fig.2 (1996); see also Pascale M. Wortley & Patricia L. Fleming, *AIDS in Women in the United States: Recent Trends*, 278 *JAMA* 911, 911 (1997). In 1993, AIDS became the fourth leading cause of death in women between the ages of 25 and 44. See *id.*

11. While lawyers and research project administrators may concentrate on the risks posed by the research, potential research subjects focus on the perceived benefits of experimental therapies and often choose to participate despite the risks. See Nancy E. Kass et al., *Trust: The Fragile Foundation of Contemporary Biomedical Research*, *HASTINGS CTR. REP.*, Sept.-Oct. 1996, at 25, 25-27. This is especially true for those suffering from life-threatening illnesses, such as AIDS. See Mary Beth Caschetta et al., *FDA Policy on Women in Drug Trials*, 329 *NEW ENG. J. MED.* 1815, 1815 (1993) ("In the particular context of AIDS, clinical trials often provide the only access to life-saving therapies for women . . ."); Merton, *supra* note 3, at 377-79; see generally Kass, *supra* note 9, at 173-74 (manuscript pages) (arguing that women as individuals and as a group are denied benefits if excluded from clinical research).

12. See, e.g., Martha F. Rogers et al., *Reducing the Risk of Prenatal HIV Transmission Through Zidovudine Therapy: Treatment Recommendations and Implications*, 50 *J. AM. MED. WOMEN'S ASS'N* 78 (1995) (reviewing the results of a clinical trial that administered zidovudine, commonly known as AZT, to HIV-infected pregnant women and their newborns). Many of the HIV and AIDS research projects that recruit women as study participants have focused not on the amelioration of women's health conditions, but rather on the transmission of the disease by HIV-infected pregnant women to their offspring. See *supra* note 8 and accompanying text.

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bearing age in clinical trials.<sup>13</sup> Are sponsors of these trials exposing themselves to the possibility of tort liability similar to that associated with DES? Or, has the tort liability barrier to the inclusion of women of childbearing age in clinical trials been broken? The purpose of this Article is to examine the tort liability experience with DES, compare it to the recent and ongoing trials of AZT in pregnant women, and extract lessons that can be used to mitigate against the likelihood of tort liability and to encourage the inclusion of women of childbearing age in clinical trials.

Part II of this Article discusses potential theories of tort liability for research-related injury. Part III briefly explores two countervailing aspects of tort liability related to women's participation in clinical trials:<sup>14</sup> (A) liability exposure resulting from injury to the offspring born of women who participated in clinical trials (that is, liability for inclusion of pregnant women and women of childbearing age); and (B) liability exposure resulting from injuries to a population as a result of the failure to test the product in that population (that is, liability for exclusion of women, or a subset of women). The analysis focuses particularly on the liability exposure of the clinical trial's sponsor because the sponsor wields considerable influence in the selection of the subject population and is likely to bear the substantial financial burden of liability. Part IV of the Article discusses the implications of the cases that arose out of the research and clinical use of DES on tort liability considerations for HIV and AIDS treatment research in women of childbearing age. Specific comparisons are made to current research and clinical use of AZT by pregnant women to prevent perinatal transmission of HIV to offspring.<sup>15</sup> Part V details the lessons that should be learned from the liability experience with DES when examining the tort liability barrier to women's inclusion in clinical trials. The Article concludes with recommendations for mitigating tort

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13. See NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14,508, 14,509 (1994) (requiring the inclusion of women in all National Institutes of Health supported research and stating that "[w]omen of childbearing potential should not be routinely excluded" from research participation); see also 62 Fed. Reg. 49,946 (1997). The FDA, for example, acknowledged its potential role in the exclusion of women from clinical research and recently proposed a rule to ensure that women of childbearing potential with life-threatening diseases will not be excluded automatically from research studies. See 62 Fed. Reg. 49,947 (1997). Under this proposed regulation, the FDA could place a clinical hold on a study if women (or men) with reproductive potential are excluded because of the trial sponsor's fear of risks to reproduction or potential offspring. See 62 Fed. Reg. 49,951. This proposed rule follows the recommendations of both the National Task Force on AIDS Drug Development and the Presidential Advisory Council on Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome. See *id.* It also reflects the recommendations of the Institute of Medicine Committee on Ethical and Legal Issues of Including Women in Clinical Studies. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 193 ("[T]he potential or prospect of becoming pregnant during the study may not be used as a justification for precluding or limiting participation.").

14. For a full exploration of tort liability issues related to women's inclusion and exclusion in clinical studies, see Flannery & Greenberg, *supra* note 4, at 91-102; 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 150-67; Merton, *supra* note 3, at 400-28; see also Clayton, *supra* note 5, at 103-10; Charo, *supra* note 5, at 144-49 (discussing the product liability fears of researchers); Rothenberg, *supra* note 5, at 1259-65 (discussing tort liability both for exclusion from, and inclusion in, research).

15. The perinatal transmission of HIV to offspring is referred to as "vertical transmission." See Joe Rhatigan et al., *Rereading Public Health, in* WOMEN, POVERTY, AND AIDS: SEX, DRUGS, AND STRUCTURAL VIOLENCE 207, 223 (Paul Farmer et al. eds., 1996) ("Vertical transmission [of HIV] from mother to child has been a topic of much study in public health research.").

liability exposure for the inclusion of women of childbearing age and pregnant women in clinical trials, including a discussion of the need for early adverse event detection and improved informed consent processes.

## II. RESEARCH-RELATED INJURIES AND TORT LIABILITY

Very little information exists regarding liability claims for research injuries.<sup>16</sup> This paucity of available data is at least partly a product of a low incidence of such injuries.<sup>17</sup> The lack of information also may reflect the reality of legal actions—that whether meritorious or not, actions often are settled or simply are not reported.<sup>18</sup> Whatever the reasons, only a very small body of case law exists relating to research injuries.<sup>19</sup>

Three theories of tort recovery potentially are applicable to a claim of research injury: battery, negligence, and strict liability.<sup>20</sup> The first, battery, is an intentional and unlawful bodily contact upon another person without that person's consent.<sup>21</sup> In the research context, a battery action could arise if an individ-

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16. See Wendy K. Mariner, *Compensation for Research Injuries*, in 2 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 117-18; 1 PRESIDENT'S COMM'N FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, COMPENSATING FOR RESEARCH INJURIES: A REPORT ON THE ETHICAL AND LEGAL IMPLICATIONS OF PROGRAMS TO REDRESS INJURIES CAUSED BY BIOMEDICAL AND BEHAVIORAL RESEARCH 2, 101 (1982) [hereinafter 1 PRESIDENT'S COMM'N] (concluding that there is insufficient data to fully resolve the question of redress for research injuries); 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 151.

17. See Mariner, *supra* note 16, at 118 (noting the "incidence of serious injury and the absolute numbers of people seriously injured are small"); 1 PRESIDENT'S COMM'N, *supra* note 16, at 65 (noting that "the incidence of serious injury and the absolute numbers of people seriously injured are small"); 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 152 ("[T]here are few reported cases of research-related injury . . ."); see also Phillippe V. Cardon et al., *Injuries to Research Subjects: A Survey of Investigators*, 295 NEW ENG. J. MED. 650, 651 (1976) (discussing a 1975 survey of principal investigators that found only about four percent of research participants had been injured, with less than one percent of those suffering permanently disabling or fatal injuries).

18. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 151; see also COMMITTEE ON CONTRACEPTIVE DEVELOPMENT, NATIONAL RESEARCH COUNCIL & INSTITUTE OF MED., DEVELOPING NEW CONTRACEPTIVES: OBSTACLES AND OPPORTUNITIES 118-46 (Luigi Mastroianni, Jr. et al. eds., 1990) (discussing products liability litigation in the context of the development of new contraceptives).

19. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 151; Rothenberg, *supra* note 5, at 1242.

20. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 153 ("The three legal bases for a legal action for research injury are battery, negligence, and strict liability."). Although the focus of this Article is sponsor liability, other defendants in a legal action arising out of a research injury may be the institution at which the trial is being conducted and the researcher or physician who provided the drug. See Clayton, *supra* note 5, at 106. In the case of injury to offspring, even a parent could be named as a defendant. See *id.* at 105-06.

21. See RESTATEMENT (SECOND) OF TORTS § 13 (1965) ("An actor is subject to liability to another for battery if (a) he acts intending to cause a harmful or offensive contact with the person of the other or a third person, or an imminent apprehension of such a contact, and (b) a harmful contact with the person of the other directly or indirectly results."); see also *Cohen v. Smith*, 648 N.E.2d 329, 335-36 (Ill. App. Ct. 1995) (reversing the trial court's dismissal of a battery complaint against a hospital and a male nurse for their failure to honor her religious beliefs against being seen unclothed by a male).

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ual were used as a research subject without her knowledge or consent.<sup>22</sup> Both compensatory and punitive damages may be awarded for battery.<sup>23</sup>

The second theory, negligence, requires the plaintiff to prove that the defendant owed the plaintiff a legal duty of care, that the defendant breached that duty, that the plaintiff suffered an injury, and that the injury was caused by the breach of the defendant's duty.<sup>24</sup> The duties owed to a research subject include the duty to provide adequate information about the potential risks of a research project<sup>25</sup> and the duty to conduct and to monitor research properly.<sup>26</sup> Negligence actions in the research context likely would raise issues concerning the duty to provide the study subject with informed consent.<sup>27</sup> The plaintiff is required to present evidence of the standard of care for informed consent (that is, what constitutes reasonable disclosure under the circumstances), that the defendant breached this standard, that the research subject would not have chosen to participate in the research project if she had known about an undisclosed risk, and that the risk caused her injury.<sup>28</sup> Negligence awards are compensatory, although in the case of extreme, or "gross" negligence, plaintiffs also may recover punitive damages,<sup>29</sup> and third parties sometimes recover damages for loss of consortium.<sup>30</sup>

The third theory of tort recovery, strict liability, does not require the plaintiff to prove the defendant's negligence.<sup>31</sup> While the second *Restatement of Torts* suggests that a manufacturer may be strictly liable if a product is sold "in a de-

22. See *Mink v. University of Chicago*, 460 F. Supp. 713, 718 (N.D. Ill. 1978) (holding that women who were given DES as a part of a medical experiment alleged sufficient lack of consent to the treatment involved to state a claim of battery); see also 1 *WOMEN AND HEALTH RESEARCH*, *supra* note 1, at 153 ("The most common application of negligence in the area of research injury is lack of informed consent.").

23. See *W. PAGE KEETON ET AL., PROSSER AND KEETON ON THE LAW OF TORTS* § 9, at 40-41 (5th ed. 1984); see also *Field v. Philadelphia Elec. Co.*, 565 A.2d 1170, 1182-83 (Pa. Super. Ct. 1989) (reversing the trial court's decision to strike plaintiff's request for punitive damages on a battery claim when an electric company knowingly exposed the plaintiff to high levels of radiation).

24. See *RESTATEMENT (SECOND) OF TORTS* § 281 (1965); *KEETON ET AL., supra* note 23, § 30, at 164-65.

25. See 21 C.F.R. § 50.25(2) (1997); see also *Gaston v. Hunter*, 588 P.2d 326, 349-51 (Ariz. Ct. App. 1978) (holding that a physician's duty, absent "exceptional circumstances," includes obtaining informed consent).

26. See 21 C.F.R. § 312.50 (1997) (requiring manufacturers to provide proper monitoring to ensure research is conducted in accord with accepted standards and study protocol).

27. See *KEETON ET AL., supra* note 23, § 32, at 189-93; see also *Flannery & Greenberg, supra* note 4, at 92; 1 *WOMEN AND HEALTH RESEARCH, supra* note 1, at 155-57.

28. See *KEETON ET AL., supra* note 23, §32, at 191.

29. See *KEETON ET AL., supra* note 23, § 2, at 9-15.

30. See *id.* § 125, at 931-33. "Loss of consortium" refers to the harm derived from losing the "sexual attentions, society, and affection" of a spouse who is injured or killed. *Id.* In addition, existing children whose parent is injured in a clinical trial might bring a loss of consortium claim. See *id.* § 125, at 935-36; *Merton, supra* note 3, at 413 (noting that "a researcher could face a loss of consortium claim from an already existing child whose parent was injured participating in the research" (citation omitted)).

31. See *RESTATEMENT (SECOND) OF TORTS* § 402A (1965); see also *Greenman v. Yuba Power Prods., Inc.*, 377 P.2d 897, 901 (Cal. 1962) ("To establish the manufacturer's liability it was sufficient that [the] plaintiff moved that he was injured while using [the product] in a way it was intended to be used as a result of a defect in design and manufacture of which [the] plaintiff was not aware that made [the product] unsafe for its intended use.").

fective condition unreasonably dangerous to the user or consumer,"<sup>32</sup> it also provides that drug manufacturers will not be liable as long as the drug, including those that are "new or experimental," is "properly prepared and marketed, and a proper warning is given."<sup>33</sup> The rationale for this caveat rests on an acknowledgment that the therapeutic benefits of drugs outweigh known and reasonable risks.<sup>34</sup> The newly-adopted third *Restatement of Torts: Products Liability* clarifies the circumstances under which prescription drug and medical device manufacturers will be held strictly liable for harm caused by their products.<sup>35</sup> Under section 6 of the third *Restatement of Torts*, a "manufacturer of a prescription drug or medical device who sells or otherwise distributes a defective drug or medical device is subject to liability for harm to persons caused by the defect."<sup>36</sup> A product may be deemed defective because of a "manufacturing defect,"<sup>37</sup> or because the product is not reasonably safe due to design<sup>38</sup> or inadequate instructions or warnings of foreseeable risks of harm.<sup>39</sup> The product must be defective at the

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32. RESTATEMENT (SECOND) OF TORTS § 402A (1965); see also *Abbott Lab. v. Lapp*, 78 F.2d 170, 176 (7th Cir. 1935) (holding a drug manufacturer liable where the drug was "in a dangerous condition at the time it was used [on the plaintiff and] . . . that condition could have caused the injury"); *Hruska v. Parke, Davis & Co.*, 6 F.2d 536, 538 (8th Cir. 1925) (holding that "an act of negligence of a manufacturer or vendor which is imminently dangerous to the life or health of mankind . . . and intended to preserve, destroy, or affect human life is actionable").

33. RESTATEMENT (SECOND) OF TORTS § 402A cmt. k (1965). In clarifying what is not an "unreasonably dangerous" product, comment k includes

many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.

*Id.*; see also *Gaston v. Hunter*, 588 P.2d 326, 340-41 (Ariz. Ct. App. 1978) (finding manufacturers of experimental drugs are not strictly liable when an adequate warning is provided).

34. See James A. Henderson, Jr., *Prescription Drug Design Liability Under the Proposed Restatement (Third) of Torts: A Reporter's Perspective*, 48 RUTGERS L. REV. 471, 473 (1996) (noting that rationale for comment k was to ensure that "the right [drugs] would reach the right patients" even though they might unavoidably cause harm).

35. See RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 8 (Proposed Final Draft Apr. 1, 1997).

36. *Id.* § 6(a). A retail seller or other distributor may be subject to liability under certain conditions as well. See *id.* § 6(e).

37. *Id.* § 2(a) ("[A] product contains a manufacturing defect when the product departs from its intended design even though all possible care was exercised in the preparation and marketing of the product . . .").

38. See *id.* § 6(c) ("A prescription drug or medical device is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health care providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients.").

39. See *id.* § 6(d) ("[R]easonable instructions or warnings regarding foreseeable risks of harm [must be] provided to: (1) prescribing and other health care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings; or (2) the patient when the manufacturer knows or has reason to know that health care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings.").



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time of sale or distribution for strict liability principles to apply.<sup>40</sup> Unlike the strict liability limitation in the second *Restatement of Torts*, the newly-revised section and its accompanying notes do not address expressly liability for drugs used in the research context.<sup>41</sup> Case law prior to the adoption of the third *Restatement*, however, suggests that the inclusion of the term “distributes” as an alternative to “sells” covers the use of drugs in the research context.<sup>42</sup>

### III. COUNTERVAILING ASPECTS OF TORT LIABILITY RELATED TO WOMEN'S PARTICIPATION IN CLINICAL TRIALS<sup>43</sup>

#### A. Tort Liability for Inclusion of Women of Childbearing Age in Clinical Trials

The informed consent process is a central feature in how research is conducted today.<sup>44</sup> This concept requires the disclosure of all facts “necessary to form the basis of an intelligent consent by the patient to the proposed treatment.”<sup>45</sup> From a clinical trial sponsor's perspective, the informed consent process not only preserves the autonomous decisionmaking of potential subjects, but also

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40. See *id.* § 6(b) (“For purposes of liability under Subsection (a), a drug or medical device is defective if at the time of sale or other distribution the drug or medical device: (1) contains a manufacturing defect as defined in § 2(a); or (2) is not reasonably safe due to defective design as defined in Subsection (c); or (3) is not reasonably safe due to inadequate instructions or warnings as defined in Subsection (d).”).

41. See *id.* § 6; cf. RESTATEMENT (SECOND) OF TORTS § 402A cmt. k (1965) (expressly addressing drugs produced for “experiment”).

42. See, e.g., *Gaston v. Hunter*, 588 P.2d 326 (Ariz. Ct. App. 1978) (rejecting manufacturer's argument that strict liability would not apply to an experimental drug because the drug was not sold).

43. The discussion herein focuses on liability for prenatal injuries, which are injuries that are alleged to have occurred to a fetus in existence at the time of the woman's ingestion of an experimental drug. These injuries could arise as a result of the participation of an already pregnant woman or a woman who became pregnant during the trial. Preconception liability—where the fetus is not in existence at the time of drug ingestion, but is alleged to have been injured—is outside the scope of this Article. It is worth noting, however, that courts have been extremely reluctant in the non-research context to allow cases of preconception liability in drug administration, as a claim would have to be made that a duty existed to a person who did not legally exist. Causation in such a case is extremely difficult to prove. See Merton, *supra* note 3, at 404-13. Rejection of this sort of claim is evidenced in the dismissal of third generation DES cases, where grandchildren of women who took DES allege injury. See, e.g., *Wood v. Eli Lilly & Co.*, 38 F.3d 510 (10th Cir. 1994); *Loerch v. Eli Lilly & Co.*, 445 N.W.2d 560 (Minn. 1989) (en banc); *Enright v. Eli Lilly & Co.*, 570 N.E.2d 198 (N.Y. 1991); *Grover v. Eli Lilly & Co.*, 591 N.E.2d 696 (Ohio 1992). But see Tracey I. Batt, *DES Third-Generation Liability: A Proximate Cause*, 18 CARDOZO L. REV. 1217, 1248 (1996) (examining the relationship between the doctrine of proximate cause generally and third-generation DES cases and suggesting recovery should sometimes be permitted). Like prenatal injuries, however, it is possible for a child born alive, or its parent, to recover for damages arising from preconceptual negligent or intentional conduct. See Merton, *supra* note 3, at 404 n.153.

44. All federally regulated or sponsored research must include informed consent of the human subject. See 56 Fed. Reg. 28,003, 28,016-17 (1991); 21 C.F.R. § 50.20, .27 (1997). In addition, all research conducted at institutions holding a Multiple Project Assurance granted by the federal government must conform to the federal regulations on informed consent. See 56 Fed. Reg. 28,014 (1991).

45. *Salgo v. Leland Stanford Jr. Univ.*, 317 P.2d 170, 181 (Cal. Dist. Ct. App. 1957). For a full exploration of the development of the concept of informed consent, see generally RUTH R. FADEN & TOM L. BEAUCHAMP, *A HISTORY AND THEORY OF INFORMED CONSENT* (1986) (providing an historical and conceptual overview of informed consent).

minimizes the sponsor's liability exposure for research injuries.<sup>46</sup> Specifically, a research subject may state a claim for battery by establishing that she never consented or knew of her participation in the study. If her initial consent were secured without adequate disclosure of risks, she may raise a claim of negligence.<sup>47</sup> If risks were known to, or were foreseeable by, the sponsor but not disclosed to the subject, the subject then could bring a strict liability action.<sup>48</sup>

The success of claims brought by, or on behalf of, offspring who were injured as a result of a mother's participation in research is less clear, because an unborn child does not have the capacity to consent to participation.<sup>49</sup> This appears to be the basis of sponsors' fear of liability for including pregnant women and women of childbearing age in clinical trials,<sup>50</sup> raising the questions of whether a mother's consent to participate in a clinical trial immunizes the sponsor against tort liability for harm to offspring and whether a woman can consent to research risks on behalf of her fetus.<sup>51</sup>

Only three reported cases involve alleged research injuries to offspring as a result of a woman's participation in a clinical study, and in all three cases the research subjects were pregnant women. Two of the cases concerned the experi-

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46. See RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. d (Proposed Final Draft Apr. 1, 1997) ("Failure to instruct or warn is the major basis of liability for manufacturers of prescription drugs and medical devices.").

47. See Flannery & Greenberg, *supra* note 4, at 92 (noting that in a negligence action, the plaintiff must show "that he or she was not given the information that should have been given and that this lack of informed consent caused the plaintiff's injury").

48. See *id.* at 93 (noting that manufacturers of products deemed "unavoidably unsafe" will not be held strictly liable for injuries caused by those products when they provide adequate warning); Charo, *supra* note 5, at 148 (noting that under strict liability, "a manufacturer can try to insulate itself from liability by giving adequate warning."); Theresa McGovern et al., *Inclusion of Women in AIDS Clinical Research: A Political and Legal Analysis*, 49 J. AM. MED. WOMEN'S ASS'N 102, 104 (1994) (suggesting that drug trial sponsors would not be held strictly liable for effects of experimental drugs provided that adequate warning is given and informed consent is obtained).

49. Outside the scope of this Article is the question of whether a federal policy promoting the inclusion of women in clinical trials would preempt state tort law claims. One could make a policy argument for such a defense from the majority's dicta in *UAW v. Johnson Controls, Inc.*, 499 U.S. 187 (1991), which argued that the federal policy promoting equal access to the workplace articulated in Title VII of the Civil Rights Act of 1964 might preempt state tort claims by a child whose mother was exposed to lead in the workplace. See *id.* at 209-10. Given the Supreme Court's refusal to find preemption except in cases where Congress explicitly intends to preempt state law or where there is a direct conflict between state and federal law, however, it is highly unlikely that a state tort claim for prenatal or preconceptional injury as a result of the mother's participation in clinical research will be preempted by federal law. See Clayton, *supra* note 5, at 103-04. For a general discussion of federal preemption, see Michael K. Carrier, *Federal Preemption of Common Law Tort Awards by the Federal Food, Drug, and Cosmetic Act*, 51 FOOD & DRUG L.J. 509 (1996).

50. See Charo, *supra* note 5, at 146 (noting that pharmaceutical manufacturers' "nervousness stems from the fact that [a] child could bring suit as a result of birth defects, since the general rule is that parents cannot waive causes of action on behalf of their children, and virtually all jurisdictions allow tort claims for prenatal injuries provided the child is born alive").

51. Phrasing the question in this way ignores the possibility that fetal effects may result from male research participation. There is a small but growing body of researchers who recognize the potential for male-mediated developmental toxicity. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 179-81 (discussing how male toxicity can contribute to adverse pregnancy outcomes).

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mental use of DES,<sup>52</sup> and the third involved the ingestion of radioactive iron.<sup>53</sup> As discussed below, none of the pregnant women in these cases were given the opportunity to consent to participate in the study, nor were they informed that they were being used as research subjects.

DES is a synthetic hormone that was prescribed widely to pregnant women from the 1940s through 1971 to prevent miscarriage.<sup>54</sup> Twenty years after its first use, researchers discovered that some of the daughters of the women who had taken the drug had developed a rare form of vaginal cancer.<sup>55</sup> By that time, at least 1.5 million offspring had been exposed to DES, and hundreds of claims arose against the manufacturers who had produced the drug.<sup>56</sup>

In the early 1950s, large controlled clinical trials of DES were conducted on pregnant women at the University of Chicago, which led to the cases of alleged research-related injury.<sup>57</sup> Both cases were brought after the discovery of the carcinogenic potential of DES in offspring of women who had been given DES.<sup>58</sup> In *Mink v. University of Chicago*,<sup>59</sup> three women, on behalf of themselves and approximately one thousand women who had participated in the trials, alleged injury, as well as increased risk of injury, to their daughters.<sup>60</sup> In *Wetherill v. Uni-*

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52. See *Wetherill v. University of Chicago*, 570 F. Supp. 1124 (N.D. Ill. 1983) (concerning women who contracted cancer that they attributed to DES administered in a medical research project to their mothers while pregnant); *Mink v. University of Chicago*, 460 F. Supp. 713, 715 (N.D. Ill. 1978) (involving pregnant women who were given DES as a part of a medical research project).

53. See *Craft v. Vanderbilt Univ.*, 940 F. Supp. 1185, 1188 (M.D. Tenn. 1996) (involving pregnant women who were the unconsenting subjects of experiments involving radioactive isotopes).

54. See Karen Weitzner & Harold L. Hirsh, *Diethylstilbestrol-Medicolegal Chronology*, 28 MED. TRIAL TECH. Q. 145, 146-49 (1982).

55. See Arthur L. Herbst et al., *Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women*, 284 NEW ENG. J. MED. 878 (1971).

56. For examples of these cases, see *Payton v. Abbott Laboratory*, 83 F.R.D. 382 (D. Mass. 1979), vacated, 100 F.R.D. 336 (D. Mass. 1983) (certifying a class action brought by women with an increased risk of cancer because of DES exposure, though the order certifying the class was later vacated); *Sindell v. Abbott Laboratory*, 607 P.2d 924 (Cal. 1980) (holding manufacturers of DES liable in proportion to their market share even though there was no evidence that they had produced the actual DES to which the plaintiffs were exposed); *McCreery v. Eli Lilly & Co.*, 150 Cal. Rptr. 730 (Cal. Ct. App. 1978) (dismissing a case brought by a woman who had been exposed to DES in utero); *Diamond v. E.R. Squibb & Sons, Inc.*, 366 So. 2d 1221 (Fla. Dist. Ct. App. 1979), quashed, 397 So. 2d 1221 (Fla. 1981) (dismissing the action of a mother who had taken DES and the claim of her daughter who had been exposed to DES in utero for failing to bring the action within the statute of limitations); *Abel v. Eli Lilly & Co.*, 289 N.W.2d 20 (Mich. Ct. App. 1980), modified, 343 N.W.2d 164 (Mich. 1984) (allowing the claim of the plaintiffs, who had been exposed to DES in utero, to go forward); *Lyons v. Premo Pharmaceutical Labs., Inc.*, 406 A.2d 185 (N.J. Super. Ct. App. Div. 1979) (dismissing action against a broker of DES); *Ferrigno v. Eli Lilly & Co.*, 420 A.2d 1305 (N.J. Super. Ct. Law Div. 1980) (shifting the burden of exculpation to the DES manufacturers). For a brief analysis of claims involving DES, see Weitzner & Hirsh, *supra* note 54, at 158-68; Romvaldo P. Eclavea, Annotation, *Products Liability: Diethylstilbestrol (DES)*, 2 A.L.R.4th 1091 (1980).

57. See *Mink v. University of Chicago*, 460 F. Supp. 713 (N.D. Ill. 1978); see also *Wetherill v. University of Chicago*, 570 F. Supp. 1124 (N.D. Ill. 1983).

58. See Weitzner & Hirsh, *supra* note 54, at 147-51.

59. 460 F. Supp. 713 (N.D. Ill. 1978).

60. See *id.* at 715. They also alleged injury to themselves and to their sons, and asked for class action certification. See *id.* at 715-16. The relationship between DES and cancer became known to the medical community in 1971, and the plaintiffs alleged that the defendants made no effort to notify the plaintiffs of their participation in the experiment until 1975 or 1976. See *id.* at 715.

versity of Chicago, the plaintiffs were two daughters who had contracted cancer that they attributed to the DES that was administered to their mothers while they were pregnant.<sup>61</sup> In both *Mink* and *Wetherill* the plaintiffs claimed that the women taking DES never knew that they were participating in an experiment or that they were even taking DES.<sup>62</sup>

In the hearing in *Mink* on whether the case brought by the mothers against the manufacturer and the institution conducting the research should be dismissed, the court held that the manufacturers had a duty to notify the women about the risks posed by DES at the time when the company became aware of them or should have become aware of them.<sup>63</sup> The court permitted the battery allegations against the University of Chicago to stand, stating that non-emergency treatment performed without consent or knowledge raises a claim of battery.<sup>64</sup> The case was settled with financial compensation to the plaintiffs and an agreement by the University of Chicago to provide medical services to women in the trials and to their offspring.<sup>65</sup> In *Wetherill*, the court permitted the daughters to bring an action against the manufacturer and the University of Chicago.<sup>66</sup> This case also settled, although the terms of the settlement were undisclosed.

Finally, a recent decision denied a motion to dismiss a claim of research injuries to offspring resulting from a clinical study of radioactive iron isotopes, referred to as Section B of the Tennessee Vanderbilt Nutrition Project. In *Craft v. Vanderbilt University*, the plaintiffs included both pregnant women and their offspring who brought an action against the organizations that sponsored the study, conducted by Vanderbilt University.<sup>67</sup> While receiving prenatal care at Vanderbilt in the late 1940s, over 800 pregnant women were given radioactive iron as a part of a study to trace iron absorption in pregnant women.<sup>68</sup> The plaintiffs maintained that they were never informed of the radioactive nature of the study or the risks of drinking the "vitamin drink" or "cocktail," or given the opportunity to refuse to participate in the research study.<sup>69</sup> The plaintiffs alleged

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61. 570 F. Supp. 1124, 1125 (N.D. Ill. 1983).

62. See *id.* at 1126-27; *Mink*, 460 F. Supp. at 715.

63. See *Mink*, 460 F. Supp. at 720. Although the court found a duty to notify, it dismissed the claims of breach of duty to warn and strict liability under Illinois tort law because the women cited risk of injury and actual injury to their offspring rather than physical injury to themselves. See *id.* at 719-20.

64. See *id.* at 715-18. Because the trial sponsors allegedly did not obtain any consent, informed consent was not at issue; if it had been, a claim of negligence would have been raised. See *id.* at 716.

65. See Caroline E. Mayer, *Getting Personal on Product Liability; Two Lawmakers' Opposing Views Stem From Their Own Painful Experiences*, WASH. POST, Mar. 7, 1995, at D1.

66. See *Wetherill*, 570 F. Supp. at 1124-31 (holding that certain expert testimony would be admissible at trial, thereby implicitly permitting plaintiffs' claims to go forward). The plaintiffs based their legal claims on battery, strict liability, breach of duty to warn, lack of informed consent, and other negligence theories. See *id.* at 1125-26.

67. 940 F. Supp. 1185, 1185-88 (M.D. Tenn. 1996). The defendants in the case were Vanderbilt University and the Rockefeller Foundation. See *id.* at 1189.

68. See *id.* at 1188-89; see also ADVISORY COMM. ON HUMAN RADIATION EXPERIMENTS, THE HUMAN RADIATION EXPERIMENTS: FINAL REPORT OF THE ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS 213-16 (1996).

69. See *Craft*, 940 F. Supp. at 1189.

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that the risk of radiation was known at the time the iron was administered, and that the results of a follow-up study conducted in the 1960s that indicated a high risk of cancer from the radioactive iron were never revealed to the study participants.<sup>70</sup> The court denied the defendants' motions to dismiss and for summary judgment.<sup>71</sup>

These cases are instructive because the courts permitted actions in battery where offspring were injured as a result of their mothers' participation in research; these cases did not involve informed consent, however, because none of the women allegedly consented to participate in the research. Thus, these cases do not establish or identify the boundaries of liability for injuries to offspring when a woman properly has consented to participate in a clinical trial.

There is, however, some support in federal regulations and in non-research-related case law concerning risks of injury to offspring for the argument that the informed consent of the mother will be sufficient to shield the sponsor from liability. Analysis of those sources suggests that the purpose of the clinical trial may be important in determining whether the sponsor will be liable, that is, whether or not the trial drug is intended to benefit the health of the mother, the fetus, both, or neither. *Roberts v. Patel*<sup>72</sup> explicitly recognized a mother's ability to consent to *medical* treatment for an unborn fetus.<sup>73</sup> *Roberts* appears to indicate that when the drug is intended to benefit the *health of the fetus*, when no negligence is involved, and when the informed consent of the woman is obtained (including a warning about the potential for risks to the fetus), the drug manufacturer will not be held liable for offspring injury.<sup>74</sup>

Federal regulations promulgated by the U.S. Department of Health and Human Services over twenty years ago, and supported by an ethical analysis by a national bioethics commission,<sup>75</sup> suggest that under certain circumstances it may be acceptable to perform research with pregnant women where the trial drug is intended solely to benefit the mother's health.<sup>76</sup> The regulations provide that research on pregnant women can be approved "where the purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs."<sup>77</sup> The regulations also require that informed consent include the possible impact of the research on the fetus.<sup>78</sup> In the same way compliance with FDA regulations is evi-

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70. See *id.* at 1190.

71. See *id.* at 1198. In November, 1996, the court ruled that the plaintiffs could proceed as a class against Vanderbilt University. See *Legal Issues: Class Action Approved in Radiation Experiment Case*, CANCER WKLY. PLUS, Dec. 9, 1996, available in 1996 WL 11464247.

72. 620 F. Supp. 323 (N.D. Ill. 1985).

73. See *id.* at 324-25 (stating "[t]his court is at a loss to say who may consent to the treatment of an unborn fetus if not the unborn fetus' parent").

74. See *id.* at 325.

75. See NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, NO. 76-127-128 RESEARCH ON THE FETUS (1975).

76. See 45 C.F.R. § 46.207 (1997).

77. 45 C.F.R. § 46.207(a)(1).

78. See 45 C.F.R. § 46.207(b). Commentators have noted that some of the provisions of this regulation are outdated, including its requirement of paternal consent. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 197; Merton, *supra* note 3, at 397 n.132. As of this writing, the federal regulations relating to research on pregnant women are under review.

dence of a manufacturer's reasonableness in marketing a drug; these regulations and the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research might be used to provide evidence for the standard of conduct of a reasonable researcher.<sup>79</sup> Following this reasoning, the best case for mitigating liability would be if the research subject were a pregnant woman with a life-threatening illness, if the woman is appropriately advised of the foreseeable risks to her and to her fetus (based on existing scientific information, including animal studies), and if the woman has no other known alternatives. This argument therefore would not support a protocol that poses very serious risks to the unborn child and offers little prospect of medical benefit to the woman.

Dicta in a 1991 Supreme Court employment discrimination case may provide additional support for asserting that the informed consent of the woman will preclude the imposition of liability. In *UAW v. Johnson Controls, Inc.*,<sup>80</sup> the company's argument for excluding women (whether pregnant or not) from jobs with potentially high levels of lead exposure was based on a fear of injury to potential children.<sup>81</sup> The Court rejected this justification for exclusion, supporting instead the autonomous decisionmaking authority of the pregnant or potentially-pregnant woman.<sup>82</sup> The Court commented that "[i]f, under general tort principles, Title VII bans sex-specific fetal-protection policies, the employer fully informs the woman of the risk, and the employer has not acted negligently, the basis for holding an employer liable seems remote at best."<sup>83</sup>

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79. See *Malek v. Lederle Labs.*, 466 N.E.2d 1038, 1039-40 (Ill. App. Ct. 1984) (holding that a jury may consider compliance with FDA regulations as evidence of reasonableness but it cannot be taken as conclusive). But see *Baldino v. Castagna*, 454 A.2d 1012, 1020 (Pa. Super. Ct. 1982), *rev'd on other grounds*, 478 A.2d 807 (Pa. 1984) ("While compliance with a law or regulation relieves the actor from liability under a theory of negligence per se, it does not establish, as a matter of law, that the actor exercised reasonable care."). Generally, however, compliance with FDA regulations in marketing a drug is not dispositive and cannot exempt or immunize a manufacturer from state tort liability. See *Hill v. Searle Labs.*, 884 F.2d 1064, 1068 (8th Cir. 1989) (holding that "FDA approval is not a shield to liability"); *Abbot v. American Cyanamid Co.*, 844 F.2d 1108, 1112-13 (4th Cir. 1988) (holding that federal law did not preempt state common-law liability for defective design or failure to warn); *Osburn v. Anchor Labs., Inc.*, 825 F.2d 908, 911-12 (5th Cir. 1987) (holding that federal statute and regulations on labeling did not preempt Texas law the on duty to warn); *Mazur v. Merck & Co.*, 742 F. Supp. 239, 247 (E.D. Pa. 1990) (holding that compliance with FDA regulation does not preempt state tort liability); *MacDonald v. Ortho Pharm. Corp.*, 475 N.E.2d 65, 70-71 (Mass. 1985) (holding that a manufacturer's compliance with FDA guidelines does not necessarily shield it from state tort liability for failing to provide adequate warnings). When an FDA requirement specifically prohibits a manufacturer from acting without FDA approval, however, compliance with FDA's strictures may preempt a state tort claim. See *Feldman v. Lederle Labs.*, 561 A.2d 288, 306-07 (N.J. Super. Ct. App. Div. 1983), *rev'd*, 592 A.2d 1176 (N.J. 1991) (holding that federal law did not clearly require FDA approval prior to a label change and thus did not preempt state law).

80. 499 U.S. 187 (1991).

81. See *id.* at 191-92.

82. See *id.* at 206-07, 211. The recommendations of the Institute of Medicine's Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies support the autonomy of all women, including pregnant women, to make decisions about participation in research and the health of their offspring. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 194-98.

83. *Johnson Controls*, 499 U.S. at 208. An argument can be made that the employment discrimination case is distinguishable because the holding is based on the interpretation of an employment discrimination statute. See *Merton*, *supra* note 3, at 423 (suggesting that paid research participation may be a form of employment.).

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Following the foregoing reasoning, liability appears to be minimized when there is adequate informed consent by the woman, which includes disclosure of possible risks to the fetus (provided, of course, that there are no other negligent actions by those in the research enterprise).<sup>84</sup> In addition, the low incidence of research injury and the difficulties in proving causation for research injury minimize the likelihood of liability imposition. Any assessment of liability exposure, however, must be balanced against considerations of possible liability for excluding women of childbearing age from clinical trials.<sup>85</sup>

### B. Tort Liability and Exclusion of Women of Childbearing Age from Clinical Trials

Liability for excluding women from clinical trials has not been addressed directly by the courts, but there is some tangential support in case law. The potential for liability for excluding women from clinical trials reflects a conceptual shift among members of the research community and the public towards participation in research. Historically, serving as a research subject was viewed as benefiting others, sometimes at significant personal risk; federal policies therefore focused on protecting subjects' rights and interests, and preventing abuse. Today, participation often offers a high likelihood of direct medical benefit, and participants now assert their "right" to enter a study.<sup>86</sup> In addition, heightened public awareness and concern about the potential impact of exclusion<sup>87</sup> likely will act to increase the probability of legal action. The specter of liability falls predominantly on the manufacturers of the experimental drugs.<sup>88</sup>

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84. Note that liability can be great where it is determined that consent is inadequate or that warnings were insufficient. See Clayton, *supra* note 5, at 104. If a child is born alive, and the mother alleges that she would not have taken the drug or chosen not to bear the child had she known about the risks, the child and the mother could assert claims for prenatal injury and economic and emotional injury, or wrongful life and wrongful birth. See *id.* Claims brought by children for wrongful life—a child is born alive, but the parents allege that more information would have led them to avoid bearing children—have been denied almost universally by courts and legislatures. See *id.* If a child was born alive, but the mother brings a claim asserting that she would have avoided childbearing if she had known more, the mother's claim would be for wrongful birth, which has the potential for large damage claims. See *id.* at 105. When a child is stillborn due to another's negligence, some jurisdictions permit the beneficiaries of the fetus' estate, usually the parents, to bring an action for wrongful death, although some states require that the fetus be viable at the time of the injury. See *id.* These claims usually result in a small amount of recovery, and many states refuse to allow them altogether. See *id.* For further discussion of prenatal injury, wrongful birth, and wrongful life, see KEETON ET AL., *supra* note 23, § 55, at 367.

85. See Flannery & Greenberg, *supra* note 4, at 94-96.

86. See *id.* at 92; Kass et al., *supra* note 3, at 41; see generally Kass, *supra* note 9, at 211 (manuscript pages) ("[W]omen now . . . have greater 'rights' to research inclusion than ever before.").

87. Reports about women's exclusion from clinical research and the risks exclusion poses have appeared in newspapers across the country. See, e.g., Bob Condor, *Rx for Women's Health: FDA Comes to Town with a Campaign to Teach Us How Medicines Affect Our Bodies*, CHI. TRIB., June 8, 1997, at 1 (describing an FDA pilot program designed to explain to women that many drugs have not been tested in women and how medication may affect them differently than it affects men); Maureen Dobie, *Clinical Drug Tests: Women Need Not Apply*, INDIANAPOLIS BUS. J., Jan. 22, 1996, at 15 ("Ignoring gender differences in body fat, hormones and muscle mass, early clinical trials here and everywhere else rely disproportionately on data collected from men.").

88. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 165 (noting that liability is an especially serious risk for manufacturers).

Liability for exclusion may arise when a woman takes a drug or treatment that was not tested on women but proves to be more dangerous or less effective in women once the drug is on the market.<sup>89</sup> The case law makes it clear that inadequate testing is a basis for imposition of liability on both negligence and strict liability principles and courts have not hesitated to evaluate research design critically and to scrutinize the activities of sponsors.<sup>90</sup> For example, in *West v. Johnson & Johnson Products, Inc.*,<sup>91</sup> damages were awarded to a woman allegedly injured as a result of using a tampon where the manufacturer failed to test the product adequately.<sup>92</sup> Similarly, in *Taylor v. Wyeth Laboratories, Inc.*,<sup>93</sup> the court found that an oral contraceptive manufacturer's potential negligence was a jury question where the manufacturer failed to examine the causal relationship suggested by studies showing that women with a particular blood type experienced a disproportionate number of adverse reactions to the drug.<sup>94</sup>

Manufacturers are at risk under strict liability principles for defective product design,<sup>95</sup> and inadequate testing may be considered a design defect.<sup>96</sup> In addition, manufacturers have a duty to warn about foreseeable risks that should have been known, a requirement that can be met only with state-of-the-art product testing.<sup>97</sup> With the current state of knowledge and sensitivity to potential physiological gender differences, an argument could be made that male-only studies do not qualify as "state-of-the-art."<sup>98</sup> The protection afforded by the third *Restatement of Torts*<sup>99</sup> and by the second *Restatement's* limitation may not be available: a manufacturer's claim that a drug is *unavoidably* unsafe may be under-

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89. See Flannery & Greenberg, *supra* note 4, at 94; see also Merton, *supra* note 3, at 419-22 (discussing the potential liability of a drug manufacturer for failing to test its products on women); Rothenberg, *supra* note 5, at 1263 (explaining the potential liability of pharmaceutical manufacturers for excluding women from clinical research).

90. In part, judicial scrutiny of the design and conduct of clinical trials may be traced to increased regulatory control of the research process exercised by the FDA. The statutory requirement that new drug approval be based on "adequate and well-controlled investigations," 21 U.S.C. § 355(d) (1994), has served to justify extensive oversight, from the form and numbers of trials needed to who may participate and how records should be kept. See generally Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1777-88 (1996) (describing the scope and practice of FDA's clinical oversight).

91. 174 Cal. App. 3d 831 (Cal. Ct. App. 1985).

92. See *id.* at 869.

93. 362 N.W.2d 293 (Mich. Ct. App. 1984).

94. See *id.* at 297; see also Wooderson v. Ortho Pharm. Corp., 681 P.2d 1038 (Kan. 1984) (awarding punitive damages where a manufacturer failed to conduct further studies after evidence of adverse effects); Barson v. E.R. Squibb & Sons, Inc., 682 P.2d 832 (Utah 1984) (holding that a manufacturer was negligent in failing to test a drug for teratogenic effects).

95. See RESTATEMENT (SECOND) OF TORTS § 402A (1965).

96. See Merton, *supra* note 3, at 416-17; Rothenberg, *supra* note 5, at 1264.

97. See Flannery & Greenberg, *supra* note 4, at 95 (quoting RESTATEMENT (SECOND) OF TORTS § 402A cmt. j (1965)); see also Shanks v. Upjohn Co., 835 P.2d 1189, 1200 (Alaska 1992) (holding that a defendant to a strict liability claim must show that risk was "scientifically unknowable at the time the product was distributed to the plaintiff").

98. See Flannery & Greenberg, *supra* note 4, at 95; Rothenberg, *supra* note 5, at 1264.

99. See *supra* text accompanying notes 35-42.



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mined if it is not tested on women but nonetheless causes harm.<sup>100</sup> A similar argument could be made concerning testing on women of childbearing age. Women in clinical trials who are counseled personally about the known risks and possibility of unknown risks of the drug to them and to their potential offspring probably are less likely to become pregnant while using the drug than women in the general population who rely on warnings found in package inserts proclaiming the unknown dangers in the event of pregnancy. In terms of medical outcome, and, therefore, potential liability, it would be more effective to monitor an unintended pregnancy and its outcome under controlled circumstances in a clinical trial setting than to allow a drug to be used by large numbers of women in the general population. The women who do not receive medical monitoring and who suffer injury to themselves or to their offspring may be more motivated to bring a legal action. These actions likely will prove costly to defend even if causation is not proven and no damages are awarded.<sup>101</sup>

## IV. COMPARATIVE ISSUES OF TORT LIABILITY: AZT AND DES

Are we destined to repeat the DES experience with AZT use by pregnant women? What risk of liability might there be in the use of AZT in research involving pregnant women? An examination and comparison of issues arising in the use of DES and AZT follows.

## A. Transplacental Carcinogenicity and AZT

Studies indicate that AZT use by an HIV-infected woman during pregnancy and by her infant after birth can reduce maternal-fetal transmission of HIV by up to two-thirds.<sup>102</sup> On the basis of such studies, the U.S. Public Health Service and professional organizations have recommended that HIV-infected pregnant

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100. An "unavoidably unsafe" product is one that is "quite incapable of being made safe for their intended and ordinary use," but which, when "properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous." RESTATEMENT (SECOND) OF TORTS § 402A cmt. k (1965).

101. About 1000 women were included in the clinical trials of DES. See *Mink*, 460 F. Supp. at 715. That number is dwarfed, however, by the claims of over 1.5 million women who were affected by DES in the *clinical* rather than the research context. See Weitzner & Hirsh, *supra* note 54, at 148. It is worth noting that the DES manufacturers ignored the results from large scale clinical trials from as early as the 1950s that indicated that the drug was ineffective; they also did not do any follow up monitoring or reporting. See *id.* at 147. The cases concerning medical use of DES are based on negligence, strict liability, violation of express and implied warranties, false and fraudulent representations, misbranding of drugs in violation of federal law, conspiracy, and lack of consent. See, e.g., *Sindell v. Abbott Labs.*, 607 P.2d 924, 926 (Cal. 1980).

102. See Centers for Disease Control & Prevention, U.S. Dep't of Health & Human Servs., *Effectiveness in Disease and Injury Prevention: Zidovudine for the Prevention of HIV Transmission from Mother to Infant*, 43 MORBIDITY & MORTALITY WKLY. REP. 285 (1994); Pamela B. Matheson et al., *Efficiency of Antenatal Zidovudine in Reducing Perinatal Transmission of Human Immunodeficiency Virus Type 1*, 2 J. INFECTIOUS DISEASES 353 (1995); Rogers et al., *supra* note 12, at 78-80. According to one study, 22.6% of HIV-infected pregnant women who did not take AZT transmitted the virus to their offspring, while only 7.6% of those who did take AZT transmitted the virus. See Rhoda S. Sperling et al., *Maternal Viral Load, Zidovudine Treatment, and the Risk of Transmission of Human Immunodeficiency Virus Type 1 from Mother to Infant*, 335 NEW ENG. J. MED. 1621, 1622-23 (1996).

women take AZT.<sup>103</sup> Because scientists suspect that AZT might have carcinogenic potential, there have been animal studies and follow-up studies in pregnant women and their offspring.<sup>104</sup> No tumors have yet been observed in human studies of approximately 1000 children who had been exposed to AZT in utero and followed for an average of three years after birth.<sup>105</sup> Preliminary results from one animal study conducted by the National Cancer Institute (NCI) indicated that very high doses of AZT during the third trimester of pregnancy increased the risk of tumors in the liver, lungs, and reproductive organs in mouse offspring.<sup>106</sup> Another mouse study utilized a different protocol and was conducted by AZT's manufacturer, Glaxo Wellcome. The results of this study indicated that AZT used during the course of pregnancy at somewhat higher doses than would be used in current clinical practice in humans, but at significantly lower levels than that of the NCI study, caused vaginal tumors in the offspring of mice exposed to AZT throughout their lifetime and resulted in no increased risk of cancer in the offspring of those mice exposed to AZT while pregnant.<sup>107</sup>

In January 1997, the National Institutes of Health (NIH) convened an independent expert panel to review the data from these studies.<sup>108</sup> The panel concluded that the two animal studies were of "uncertain relevance" to humans.<sup>109</sup> Nonetheless, the panel (1) identified the need for further research in this area, and specified research priorities; (2) specified the need for counseling pregnant women about the possible cancer risk in offspring in clinical trials and clinical practice; (3) emphasized the need for long-term follow-up of all exposed offspring, including those who were not infected with HIV; and (4) recommended reassessment of the Public Health Service's clinical practice guidelines.<sup>110</sup> Overall, the panel concluded that the "known benefits of AZT in preventing perinatal transmission appear to far outweigh the hypothetical concerns of transplacental carcinogenesis raised by the NCI mouse study."<sup>111</sup>

#### B. AZT versus DES

As AZT becomes accepted as the commonly-prescribed therapy for reducing the risk of perinatal HIV transmission, the potential for cancer in offspring raises the specter of DES liability. The key factors that distinguish research experience with AZT in pregnant women from that of DES are (1) the drug's purpose, the woman's health status, and the intended beneficiaries of the drug; (2) in the

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103. See Centers for Disease Control & Prevention, U.S. Dep't of Health & Human Servs., *Recommendations of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus*, MORBIDITY & MORTALITY WKLY. REP.: RECOMMENDATIONS AND REPORTS, Aug. 5, 1994, at 1, 1-20; Rogers et al., *supra* note 12, at 80-81.

104. See Office of Communications, National Inst. of Health, *Fact Sheet: Summary of the Meeting of a Panel to Review Studies of Transplacental Toxicity of AZT* (visited Oct. 27, 1997) <<http://www.niaid.nih.gov/factsheets/aztsumm.htm>>.

105. See *id.*

106. See *id.*

107. See *id.*

108. See *id.*

109. See *id.*

110. See *id.*

111. See *id.*

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clinical trial, the woman's consent, warnings of potential known and unknown fetal risks, and monitoring and follow-up of the study population; and (3) in clinical practice, the provision of warnings of potential risks to the woman and/or fetus and notification of results of new research studies.<sup>112</sup> The way in which these factors are addressed likely will impact the potential liability for offspring injury. Table 1 below briefly compares these factors with respect to the use of AZT and DES by pregnant women in clinical trials and clinical practice. When considered side-by-side, the contrast in the experience with DES and AZT is stark.

TABLE 1: COMPARISON OF DES AND AZT IN CLINICAL TRIALS AND CLINICAL PRACTICE — PREGNANT WOMEN

	DES	AZT
Purpose	Prevention of miscarriage <sup>a</sup>	Prevention of perinatal HIV transmission
Woman's Health	Healthy	Life threatening disease
Beneficiary of potential direct health benefits	Child, and woman's mental health	Woman and child
Clinical Trials: Consent of Woman?	No <sup>b</sup>	Yes <sup>c</sup>
Clinical Trials: Warning of potential known and unknown risks to fetus?	No <sup>b</sup>	Yes <sup>d</sup>
Clinical Trials: Monitoring and follow up	No <sup>b</sup>	Yes, in children and women <sup>d</sup>
Clinical Trial: Additional Research	No <sup>b</sup>	Yes, in animals <sup>d</sup>
Clinical Practice: Warning of potential risk to woman and/or fetus	No <sup>b</sup>	Yes <sup>d</sup>
Clinical Practice: Notification of results of new studies?	No <sup>b</sup>	Yes, reassessing clinical guidelines, alerting to possible cancer risk <sup>d</sup>

Notes:

a. See *supra* note 54 and accompanying text. Note that the manufacturers ignored the results from large scale clinical trials as early as the 1950s that indicated that the drug was ineffective for this purpose. See *supra* note 101.

b. See *Wetherill v. University of Chicago*, 565 F. Supp. 1124 (N.D. Ill. 1983); *Mink v. University of Chicago*, 460 F. Supp. 713 (N.D. Ill. 1978); see also *Weitzner & Hirsch*, *supra* note 54, at 146-47.

c. This is presumed because informed consent is now a regulatory requirement of performing research. See *supra* note 44.

d. These are all recommendations made by a review panel convened by the National Institutes of Health. See Office of Communications, *supra* note 104. The extent to which these recommendations are being implemented is unclear.

112. See *supra* Parts III, IV.

In light of the NIH panel's recommendations, it is unclear how and whether information about risks is being conveyed to pregnant women who formerly received, or currently are receiving, AZT. If information is not communicated properly, it raises the potential for liability in negligence and strict liability.<sup>113</sup> If the recommendations concerning communication of risk and reevaluation of clinical practice guidelines are in fact implemented, however, risks of liability likely would be minimized in the case of AZT; the elements of consent, monitoring, additional research, and dissemination of information clearly distinguish research experience with AZT in pregnant women from that of DES.

#### V. LESSONS FROM DES FOR REDUCING POTENTIAL LIABILITY

Adverse reactions to experimental drugs and devices will occur despite the best preclinical testing.<sup>114</sup> Imposition of tort liability is just one approach to compensate for these research-related injuries.<sup>115</sup> Nationally recognized expert bodies have recommended mandatory no-fault compensation systems<sup>116</sup> and inclusion of medical care reimbursement for research-related injuries in health care reform efforts.<sup>117</sup> Private approaches include contractual models and voluntary adoption of compensation plans.<sup>118</sup> These public policy alternatives, however, are unlikely to be adopted in the near future, and private approaches are employed infrequently.<sup>119</sup> Without alternatives, tort liability, or the threat thereof, is left as the only realistic action for those seeking compensation for research injuries.

There are at least three lessons to be learned from the liability experience with DES that should be considered in addressing the tort liability barrier that women of childbearing age face in accessing research and experimental therapies.

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113. See discussion *supra* Part II.

114. See 1 PRESIDENT'S COMM'N, *supra* note 16, at 9.

115. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 243-52; Mariner, *supra* note 16, at 113-26 (discussing various compensation models and their rationale).

116. See 1 PRESIDENT'S COMM'N, *supra* note 16, at 113-49 (explaining the desirability of a no-fault system and the various no-fault models); 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 169 (recommending that the NIH review current health care compensation systems with special attention to prenatal and preconceptual injuries to children resulting from parent's participation in clinical studies); see also ADVISORY COMM. ON HUMAN RADIATION EXPERIMENTS, *supra* note 68, at 528-29 (referring to the recommendations of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Compensating for Research Injuries: A Report on the Ethical and Legal Implications of Programs to Redress Injuries Caused by Biomedical and Behavioral Research*).

117. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 169 (noting that the current health care reimbursement system excludes coverage for medical expenses sustained during research, and suggesting that a system of universal access with adequate coverage is needed for these costs).

118. Under the contractual model, the research institute agrees to pay for medical care and other specific losses caused by research injuries in exchange for a waiver of the subjects right to sue. See Mariner, *supra* note 16, at 123. Voluntary compensation plans include research institutes purchasing liability insurance. See *id.* at 123-24.

119. Most research institutions require research subjects to rely on medical insurance coverage to reimburse costs that are incurred to treat research-related injuries. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 169.

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First, *the risk of liability for including women of childbearing age in clinical trials is quite small when compared to the potential for substantial liability when a drug is released into the general population and used by women of childbearing age without first being tested on this group.* Clinical trial sponsors cannot escape the reach of tort liability by excluding women of childbearing age from research; sponsors will have to counterbalance liability exposure associated with offspring injury resulting from inclusion of women of childbearing age in clinical trials with liability exposure that arises when a drug is prescribed in clinical practice in a population of women of childbearing age in whom the drug has not been tested adequately. Excluding these women and ignoring the possibility that they may be, or may become, pregnant while taking a marketed drug is naive. The numerous legal actions, the number of women affected, and the magnitude of recovery for the clinical use of DES far exceeded that which arose from the research use of DES or that which could have arisen had there been adequate informed consent in the research studies.<sup>120</sup>

Second, *early adverse event detection reduces the number of children who will be exposed to the drug in the future, which will result in a corresponding reduction in the magnitude of liability exposure.*<sup>121</sup> An argument could be made to support claims of negligence and strict liability on grounds of failure to warn or failure to test adequately and that risks to offspring based on a mother's exposure to a particular drug are reasonably foreseeable in the general population.<sup>122</sup> This is especially true where a drug is intended to preserve pregnancy and the health of the fetus (DES) or to protect the health of the mother and the fetus (AZT), as one can argue that the "fetus can be seen as an intended beneficiary of the drug and a foreseeable victim of injury."<sup>123</sup> With strict liability claims, the sponsor will not be responsible for such harms unless they were known at the time of distribution.<sup>124</sup> If such adverse events are discovered quickly and are made public, fewer injuries will occur in the future, and it is less likely that the sponsor will face a claim that a reasonable drug company would have discovered the effects in offspring earlier. The difficulty is that the potential for mutagenic<sup>125</sup> or teratogenic<sup>126</sup> effects may be low or may manifested only after a long latent period.<sup>127</sup> At least three steps could be taken to reduce liability exposure for offspring injury in both the research and clinical use populations: (1) conduct animal reproductive studies and continue these studies following drug distribution in the general

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120. See *Mink v. University of Chicago*, 460 F. Supp. 713, 713 (N.D. Ill. 1978); Weitzner & Hirsh, *supra* note 54, at 148.

121. As a matter of common sense, if the number of children exposed to a drug is reduced, the number of potential plaintiffs also is reduced in the event that such a drug is determined to cause injury.

122. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. g (Proposed Final Draft Apr. 1, 1997) ("Drug and medical device manufacturers have responsibility to perform reasonable testing prior to marketing a product and to discover risks and risk avoidance measures that such testing would reveal."); see also *id.* illus. 2-3.

123. Mariner, *supra* note 16, at 119.

124. See *supra* notes 35-40 and accompanying text.

125. A mutagen is an "agent . . . that promotes a mutation." STEDMAN'S MED. DICTIONARY 1160 (20th ed. 1995).

126. A teratogen "causes abnormal fetal development." *Id.* at 1771.

127. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 167.

population;<sup>128</sup> (2) initiate long-term medical follow-up in offspring of clinical trial participants who became pregnant during research participation;<sup>129</sup> and (3) continue post-marketing surveillance in the general population of users.<sup>130</sup> If such efforts are undertaken, it would be difficult to argue that a reasonable drug company could have discovered the effects in offspring earlier.<sup>131</sup>

These approaches raise practical issues in need of resolution. Mechanisms need to be developed to locate and to maintain long-term contact with study participants and their offspring. Pregnant women and women of childbearing age should be notified of the potential for ongoing evaluation of their offspring as part of the informed consent process when they are advised that long-term and short-term risks to offspring are not yet known. Steps need to be taken to improve awareness of post-marketing surveillance efforts, including establishing registries among HIV-infected pregnant women, their offspring, and their health care providers.<sup>132</sup> Locating offspring for post-trial and post-marketing surveillance raises particularly vexing issues in the HIV-infected population: if a mother succumbs to the disease, her children may be orphaned and difficult to locate.<sup>133</sup> In addition, the demographics of HIV-infected women indicate that they and their children may be less likely to have access to regular medical care that would facilitate such follow-up.<sup>134</sup>

How does a sponsor determine the point at which scientific conclusions from ongoing research and monitoring become foreseeable risks that would require a duty to warn clinical and research populations?<sup>135</sup> This question is no different for harm that potentially may affect offspring than for any other affected

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128. Current regulations do not require that animal reproduction studies be conducted for a drug to be approved. See Merton, *supra* note 3, at 66.

129. See Office of Communications, *supra* note 104 (recommending that researchers follow-up on children exposed to AZT in utero).

130. See Ruth B. Merkatz, *Women in Clinical Trials of New Drugs: A Change in Food and Drug Administration Policy*, 329 NEW ENG. J. MED. 292, 295 (1993) (recommending the "systemic collection of postmarketing exposure data").

131. See RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. g, illus. 2-3 (Proposed Final Draft Apr. 1, 1997).

132. See Office of Communications, *supra* note 104 (recommending improved efforts to ensure awareness of the industry-sponsored Antiretroviral Pregnancy Registry).

133. See Lawrence Wissow et al., *Psychosocial Issues for Children Born to HIV-Infected Mothers*, in HIV, AIDS, AND CHILDBEARING 78, 87 (Ruth R. Faden & Nancy E. Kass eds., 1996) (noting that "[c]hildren born into HIV-infected families face a greater than average risk that they will experience the death of a parent or sibling").

134. Rates of HIV and AIDS in women are highest in urban areas where access to care is limited. See Lois Eldred & Richard Chaisson, *The Clinical Course of HIV Infection in Women*, in HIV, AIDS, AND CHILDBEARING, *supra* note 133, at 15, 24.

135. One commentator has argued that "establishing surveillance systems, or requiring companies to keep track of and report adverse drug reactions, may provide plaintiffs with a source of evidence that a company knew or should have known that a particular drug or dose level was potentially dangerous and required further testing or a more adequate warning label." 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 167 (citing Jeffrey N. Giffs & Bruce F. Mackler, *Food and Drug Administration Regulation and Products Liability: Strong Sword, Weak Shield*, 22 TORT & INS. L.J. 194, 237-40 (1987)). This is contrary to the common sense principle articulated herein that identifying those who suffer adverse reactions as soon as possible limits potential liability because it limits the number of actions a company eventually may be forced to defend. See *supra* notes 120-30 and accompanying text.

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population, as experience with AZT points out. As discussed earlier, an independent panel of the National Institutes of Health was convened to review the data from two animal studies.<sup>136</sup> The panel stressed the need for counseling all HIV-infected pregnant women in clinical practice or in clinical trials about the risk of AZT treatment interventions, advocated a thorough reassessment of the Public Health Service guidelines on the use of AZT to reduce the risk of perinatally-acquired HIV infection, and identified additional research priorities.<sup>137</sup> Sponsors may not only want to conduct their own studies, but also may want to convene independent panels to review data as it emerges to ensure that they are meeting a reasonableness standard that will not be judged harshly in court.

Once a foreseeable risk is established, whether through post-trial or post-marketing surveillance, the study and clinical population must be reached through medical alerts and directives, which must be tailored to the population that they are intended to benefit. For example, sponsors should consider whether the standard approaches through the "learned intermediary"<sup>138</sup> are acceptable in light of the population using the drug. HIV-infected women and their offspring may not have access to regular medical care.<sup>139</sup> Perhaps more important to minimizing liability exposure, strategies need to be developed to identify and to notify the population of offspring exposed to AZT who may have been orphaned at an early age and who were fortunate not to have contracted the disease through perinatal transmission. This population is likely to be lost easily in follow-up.<sup>140</sup>

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136. See Office of Communications, *supra* note 104.

137. See *id.* The panel also concluded that there was a need for long-term follow up of all children exposed in utero, including those who were not infected with HIV. See *id.*

138. The "learned intermediary rule" is a common law doctrine holding that a physician, the "learned intermediary" is responsible for providing a prospective patient with sufficient warning of the risks attendant to using a drug. The doctrine provides the drug's manufacturer with a defense against liability for failure to warn so long as the provider fully informs the physician of the drug's risks. See *DeLuryea v. Winthrop Labs.*, 697 F.2d 222, 225 (8th Cir. 1983); *Lindsay v. Ortho Pharm. Corp.*, 637 F.2d 87, 91 (2d Cir. 1980); *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1362 (4th Cir. 1975); *Martin v. Hacker*, 628 N.E.2d 1308 (N.Y. 1993); cf. KEETON ET AL., *supra* note 23, § 96, at 688. The rationale for the "learned intermediary rule" is as follows:

The obligation of a manufacturer to warn about risks attendant to the use of drugs and medical devices that may be sold only pursuant to a health care provider's prescription traditionally has required warnings directed to the health care provider and not the patient. The rationale supporting this "learned intermediary" rule is that only health care professionals are in a position to understand the significance of the risks involved and to assess the relative advantages and disadvantages of a given form of prescription-based therapy. The duty then devolves on the health care provider to supply to the patient such information as is deemed appropriate under the circumstances so that the patient can make an informed choice as to therapy. . . . However, in certain limited therapeutic relationships the physician or other health care provider has a much diminished role as an evaluator or decisionmaker. In these instances it may be appropriate to impose on the manufacturer the duty to warn the patient directly.

RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. b (Proposed Final Draft Apr. 1, 1997).

139. See Liza Solomon & Sylvia Cohn, *Access To, and Utilization of, Health Services for HIV-Infected Women*, in HIV, AIDS, AND CHILDBEARING, *supra* note 133, at 96, 96-109.

140. Because AIDS is a leading cause of death among young women, a substantial number of children become orphans within a few years of their mother's diagnosis. See Alfred Saah, *The Epidemiology of HIV and AIDS in Women*, in HIV, AIDS, AND CHILDBEARING, *supra* note 133, at 1, 7 (noting that "[d]eath in this age group is particularly devastating to children who are orphaned").

Third, *adequate warnings provided during the informed consent process should greatly reduce the likelihood of recovery in a tort action.* General legal theories of liability and case law in both the research and the clinical contexts indicate that adequate informed consent is paramount to minimizing the risk of a successful legal action for research injury.<sup>141</sup> The Institute of Medicine's Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies provided comprehensive guidance on information that should be incorporated into the informed consent process when women (and men) of reproductive age, lactating women, and pregnant women participate in clinical trials.<sup>142</sup> For women and men of reproductive age, such information includes risks to reproduction and potential offspring, and, where appropriate, discussions of birth control and pregnancy termination options.<sup>143</sup> For lactating women, the consent process includes the notification and identification, if possible, of risks to offspring.<sup>144</sup> Finally, for pregnant women, adequate information includes evaluating risks and benefits to themselves, their pregnancies, and their potential offspring.<sup>145</sup> Pregnant women also should be urged to consult their obstetrical care providers before they participate.<sup>146</sup> As with all research, an interactive consent process with the potential research subject, rather than sole reliance on a signed consent form, improves the meaningfulness and quality of the informed consent process.<sup>147</sup> These additional actions are important especially when the perception of liability exposure is considered to be high.

It is disturbing that some informed consent processes lack even the minimum of information described above. One review of informed consent documents in thirty-six AIDS clinical trials indicated that only seventeen percent provided information about known teratogenic risk and that specific directions were not provided should a pregnancy occur during the clinical trial.<sup>148</sup> Because institutions, institutional review boards, and researchers could be held accountable for missteps in the informed consent process, clinical trial sponsors have a strong incentive to develop effective strategies to communicate this important information to the research subjects through these other parties.

The potentially-significant benefit of these actions should not be underestimated. Studies outside the clinical trial context underscore the impact of good communication between providers and patients in reducing the likelihood of

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141. See *supra* Part III.

142. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 1, at 191-97.

143. See *id.* at 193-94.

144. See *id.* at 194.

145. See *id.* at 195-97.

146. See *id.* at 196.

147. See *id.* at 196-97 (describing an interactive process that might help a pregnant woman understand the risks of research); see also FADEN & BEAUCHAMP, *supra* note 45, at 306-07 ("The key to effective communication is to invite active participation by patients or subjects in the context of an informational exchange.").

148. See McGovern et al., *supra* note 48, at 103.



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malpractice claims.<sup>149</sup> Although no studies have evaluated liability exposure reduction for research injury and the role of the relationship between the research subject and the investigators, institutions, or sponsors, studies have indicated the importance of the trust relationship between the subject and those conducting studies in motivating people to participate in clinical studies.<sup>150</sup> Building on and solidifying this relationship may be valuable in reducing liability exposure for research injury.

## VI. CONCLUSION

Tort liability for inclusion of women in clinical trials is just one of the potential barriers hindering advances in women's health, as well as the health of society as a whole. Earlier inclusion of women of childbearing age in HIV and AIDS research would have prevented serious harm to women's health and reduced the burden on the health care system of treating HIV-infected women, their partners, and their children.<sup>151</sup> In addition to balancing the risk of liability for inclusion against liability for exclusion, steps can be taken to minimize liability exposure. It is imperative that follow-up studies in offspring and ongoing monitoring be conducted and that information on risk be communicated immediately to all those affected by participation in clinical trials. While trials must be constructed and monitored carefully in order to address the tort liability barrier, the search for a cure simply cannot exclude women.

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149. See Howard B. Beckman et al., *The Doctor-Patient Relationship and Malpractice: Lessons from Plaintiff Depositions*, 154 ARCHIVES INTERNAL MED. 1365, 1368 (1994) (suggesting that the probability of a suit is increased by ineffective physician communication); Wendy Levinson et al., *Physician-Patient Communication: The Relationship with Malpractice Claims Among Primary Care Physicians and Surgeons*, 277 JAMA 553, 557 (1997) (indicating that communication affects the likelihood of malpractice claims against primary care physicians, although not against surgeons); Wendy Levinson, Editorial, *Physician-Patient Communication: A Key To Malpractice Prevention*, 272 JAMA 1619, 1619-20 (1994) (citing multiple studies suggesting that breakdowns in communication between physician and patient influence positively a patient's decision to file a malpractice claim).

150. See Kass et al., *supra* note 11, at 25, 26; see also ADVISORY COMM. ON HUMAN RADIATION EXPERIMENTS, *supra* note 68, at 459-81 (describing the attitudes of research subjects toward medical research).

151. See Centers for Disease Control & Prevention, *Update: Perinatally Acquired HIV/AIDS—United States, 1997*, 278 JAMA 2135, 2135-36 (1997) ("Perinatal transmission of [HIV] accounts for virtually all new HIV infections in children.").