COMMENT

GENDER BIAS IN CLINICAL DRUG TRIALS

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I. INTRODUCTION

Pharmaceutical drugs are an everyday part of American life. Along with a multitude of over-the-counter remedies, 59% of Americans have at least one prescription medication for everything from mundane necessities to life-threatening illnesses.[2] Whatever the medical complaint, many individuals' first thought is to wonder, "Do they have a prescription for that?"

This reliance on pharmaceutical remedies comes with risks. We are taught from an early age that these pills and tinctures can be dangerous if abused,[3] and potentially hazardous even if taken correctly. The average patient is vaguely aware that we use clinical drug trials to measure those hazards. Because of the sheer scope of the clinical testing system—there are well over 250,000 current trials as of this writing[4]—a person might reasonably expect that any drug their doctor prescribes has been thoroughly studied and has predictable effects.

For women,[5] this comfortable assumption was for a long time essentially false – and even today may not be as true as it should be. Historically, drug trials were generally done almost exclusively on male subjects, and many drugs on the market today were approved before the rules changed.[6] Even now, women's participation in stage 1 clinical trials lags noticeably behind that of men. Although women are reasonably well represented in much stage 2 and 3 testing, and even over represented in certain areas, the most recent data suggests women still only make up 22% of phase 1 trial participants.[7] Research into this subject is complicated by around 9% of published studies that fail to report participant gender.[8]

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2. Brady Dennis, *Nearly 60 Percent of Americans—the Highest Ever—are Taking Prescription Drugs*, WASH. POST (Nov. 3, 2015), https://www.washingtonpost.com/news/to-your-health/wp/2015/11/03/more-americans-than-ever-are-taking-prescription-drugs/?utm_term=.caef199d81c1 [perma.cc/33GU-8JGL] (explaining that there has been a sharp uptick in recent years, attributed to obesity and that many of the drugs are used to treat obesity-related ailments like hypertension).

3. *See, e.g., Vintage 80's We're Not Candy PSA Commercial with Singing Pills*, YOUTUBE.COM, https://youtu.be/e3zds9zaDBc [https://perma.cc/J6SK-U4N9] (last visited March 13, 2018) (a classic 1980s public service announcement).

4. *See, e.g.,* U.S. National Library of Medicine, *ClinicalTrials.gov*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ [https://perma.cc/S5ZE-32RV] (keeping an updated list of clinical trials).

5. Although this paper will use the term 'women' for brevity's sake, most of the problems described apply to any female-bodied individual, regardless of gender identity. For a better overview of the interplay between sex and gender in the medical research context, this author recommends Eugenia Morselli et al., *Sex and Gender: Critical Variables in Pre-Clinical and Medical Research*, 24 CELL METABOLISM 203, 203 (2016).

6. Of course, older drugs can be reexamined. However, for reasons that will be discussed later in this comment, catching side effects of a drug becomes much harder once it reaches the marketplace.

7. Geert Labots et al., *Gender Differneces in Clinical Registration Trials: Is there a Real Problem?*, BRIT. J. OF CLINICAL PHARMACOLOGY (forthcoming 2018) (draft version available at http://onlinelibrary.wiley.com/doi/10.1111/bcp.13497/epdf).

8. *Id*.

This article will begin by exploring why this gender gap matters and why it exists in the first place. Initially excluded from most clinical trials by informal custom, this later became formal policy out of concern about potential fetal deformities.[9] The FDA did not change its rules until studies revealed that relying on male-only testing led to "drug doses for women [that] were sometimes wrong, to the point that they made the drugs useless or worse."[10] For example, exclusion made it difficult to predict how drugs might interact with oral contraceptives.[11] However well-intentioned the ban on female participation might have been, it ignored a basic reality: women will still turn to pharmaceutical remedies, whether they are included in the clinical trials or not.

The problem with this bias is that male and female bodies have differences down to the cellular level that often translate to different pharmacokinetic and pharmacodynamic reactions to drugs. This can have real consequences for women, who are 50 to 75 percent more likely to experience serious drug complications than men.[12] This danger is magnified by women significantly outpacing men in prescription drug use.[13] Between 1999 and 2010, the mortality rates for prescription drug overdoses in women rose a startling 400 percent—substantially more than the 250 percent increase in men.[14] Since 2007, women have been more likely to die from a drug mishap than an automobile accident.[15]

This article will argue that researchers should require researchers to test on their expected market demographics from stage 1 trials onward whenever practicable. If a medication treats a condition from which women rarely suffer, exclusion of women from trials is appropriate. If the condition is a fifty-fifty split, women should make up half the clinical trial group. Additionally, reports on clinical trials should be required to include information about participant gender.

This article will also analyze a recently proposed Congressional reaction to the clinical trial gender gap. S.2745 ("Advancing NIH Strategic Planning and Representation in Medical Research Act") was proposed in early 2016. Its

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9. Philip Hilts, *FDA Ends Ban on Women in Drug Testing*, N.Y. TIMES (Mar. 25, 1993), http://www.nytimes.com/1993/03/25/us/fda-ends-ban-on-women-in-drug-testing.html [perma.cc/6ZY5-PZW4].

10. *Id*.

11. *Id*.

12. Marius Rademaker, *Do Women have more Adverse Drug Reactions?* 2 AM. J. OF CLINICAL DERMATOLOGY 349, 349 (2001).

13. To be precise, the pharmaceutical consumption gap arises from the mid-thirties on, with women using nearly double the prescriptions as men from 85+. From early childhood to the early twenties, men use more medication than women. NAT'L CEN. FOR HEALTH STATS., HEALTH, UNITED STATES, 2015: WITH SPECIAL FEATURE ON RACIAL AND ETHNIC HEALTH DISPARITIES 272 (2016).

14. CEN. FOR DISEASE CONTROL, VITAL SIGNS: OVERDOSES OF PRESCRIPTION OPIOID PAIN RELIEVERS AND OTHER DRUGS AMONG WOMEN – UNITED STATES, 1999-2010 (2013), https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6226a3.htm [https://perma.cc/FRX8-7TV7].

15. *Id*.

authors wanted the National Institutes of Health (NIH) to work out an action plan for addressing the lingering inequality. The bill indicated that the authors expected the NIH to incentivize researchers to address the gap.

However, the fleet of proposed legislation to which S.2745 belonged was passed into law in December of 2016 as the 21st Century Cures Act – without S.2475. Indeed, the ultimate result of Congress's 2016 interest in biomedical research was to reduce the regulatory burden on clinical trials, not increase it.[16] The current Presidential administration has indicated that their commitment is likewise to reduce the overall regulatory burden,[17] and it seems unlikely that concerns for women's health will put a damper on this trend.

It has been two decades since the FDA changed its policy on women in clinical drug trials and began to push for inclusion.[18] Despite this, change has been slow. In 2004, women made up less than one-quarter of all patients enrolled in 46 examined clinical trials.[19] More recent data suggests gender parity in stage 2 and 3 trials, but women remain under represented during stage 1 testing.[20]

By making it mandatory to conduct clinical drug trials on their anticipated usage demographics from the start,[21] researchers will be able to spot problems and fine-tune dosages earlier. While this will create costlier trials, the long-term benefits outweigh the downsides—including for pharmaceutical companies, who will likely avoid substantial liability.

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16. Mike DeBonis, *Congres Passes 21st Century Cures Act, Boosting Research and Easing Drug Approvals*, WASH. POST (Dec. 7, 2016), https://www.washingtonpost.com/news/powerpost/wp/2016/12/07/congress-passes-21st-century-cures-act-boosting-research-and-easing-drug-approvals/?utm_term=.1ebfee2d7dc5 [perma.cc/E8H5-EPBM].

17. *See e.g.* Clyde Wayne Crews Jr., *Donald Trump Promises To Eliminate Two Regulations For Every One Enacted*, FORBES (Nov, 22, 2016, 12:12 PM), https://www.forbes.com/sites/waynecrews/2016/11/22/donald-trump-promises-to-eliminate-two-regulations-for-every-one-enacted/#6efe63445864.

18. *Evaluation of Gender Differences in Clinical Investigations – Informational Sheet*, U.S. FOOD & DRUG ADMINISTRATION, https://www.fda.gov/RegulatoryInformation/Guidances/ucm126552.htm.

19. Stacie E. Geller et al., *Adherence to Federal Guidelines for Reporting of Sex and Race/Ethnicity in Clinical Trials*, 15 J. OF WOMEN'S HEATH 1123, 1123 (2007).

20. Labots, *supra* note 7.

21. While this article is focused on women and prescription drugs, drug reactions can also vary by race and ethnicity, and many of the arguments in this paper could apply just as well—and often better—when it comes to racial diversity in all stages of clinical drug trials. Different racial and ethnic groups can have important differences in drug reactions. For example, African-American women have been shown in several studies to have slower resting metabolisms than white women, which impacts how long a drug stays in the system. Valentine Burroughts et al., *Racial and Ethnic Differences in Response to Medicines: Towards Individualized Pharmaceutical Treatment*, 94 J. OF THE NAT'L MED. ASSOC., no. 10, Oct. 2002, at 1, 8.

II. CLINICAL DRUG TRIALS AND WOMEN – THE SCIENCE PROBLEM

For researchers, women in clinical drug trials are an uncomfortable balancing act. On the one hand, if a drug impacts male and female bodies differently, it is in everyone's best interest—from the manufacturers on down through the patients themselves—to know as soon as possible. On the other hand, there are cultural, biomedical, and socioeconomic reasons why male participants have been traditionally favored.

A. Male and Female Bodies Inherently React to Drugs Differently

It is important to start with a ground floor fact: drugs frequently impact women differently. Why? There is no single possible reason why women and men might react differently to the same chemical combination. Instead, the explanations can be broken into two main groups: pharmacokinetic and pharmacodynamic. Pharmacokinetic reasons stem from how the body's own systems impair or enhance a drug's effectiveness: how the body affects the drug.[22] Pharmacodynamic reasons stem from how a drug impairs or enhances those systems in turn: how the drug affects the body.[23]

The most intuitive pharmacokinetic reason is the easiest to spot: women are, overall, the smaller sex.[24] Smaller people have less body mass to diffuse a dosage: if two people with differing body masses take the same pill, the smaller person gets a more concentrated dose by default.[25] To account for differences in

22. Jennifer Le, *Overview of Pharmacokinetics*, MERCK MANUALS. http://www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/overview-of-pharmacokinetics [https://perma.cc/C8EE-N7FD].

23. Abimbola Farinde, *Overview of Pharmacodynamics*, MERCK MANUALS. http://www.merckmanuals.com/professional/clinical-pharmacology/pharmacodynamics/overview-of-pharmacodynamics [https://perma.cc/67WL-RNNK].

24. Anders Gustafsson & Patrik Lindenfors, *Human Size Evolution: No Allometric Relationship between Male and Female Stature*, 47 J. OF HUMAN EVOLUTION 253, 253 (2004). Among many possible explanations: women normally have two X chromosomes, and thus get a double dose of *ITM2A,* a gene that appears to negatively impact height via cartilage development. Taru Tukiainen et al., *Chrimosome X-Wide Association Study Identifies Loci for Fasting Insulin and Height and Evidence of Incomplete Dosage Compensation*, 10 PLOS Genetics 1, 8 (2014). The authors observe that the X chromosome hypothesis is still somewhat speculative: there have been very few studies on the X chromosome, possibly for the same reasons women are routinely excluded from clinical trials. See generally *Tukiainen et al., Chrimosome X-Wide Association Study Identifies Loci for Fasting Insulin and Height and Evidence of Incomplete Dosage Compensation.*

25. *See* Heather Whitley & Wesley Lindsey, *Sex Based Differences in Drug Activity*, 80 AM. FAM. PHYSICIAN 1254, 1255 (2009).

body mass, physicians consult tables recommending different dosages for men and women.[26]

Additionally, women have slower gastrointestinal motility: food (and drugs) take a longer time to wind through a woman's digestive system.[27] Generally, medications come with food requirements, such as an empty or full stomach. If a drug must be taken on an empty stomach to avoid negative reactions, women may need to wait longer between eating and taking the drug.[28] Once a drug hits the intestines, it may be impacted by women's lower intestinal enzymatic activity; it simply takes longer for a woman's intestines to do their job.[29] Women likewise have a slower glomerular filtration rate, which means their kidneys function slower than males.[30]

The reasons for pharmacodynamic differences are less well understood.[31] Women have been shown to be more sensitive than men to beta-blockers and opioids.[32] Women are also more sensitive to certain serotonin reuptake inhibitors as well as most antipsychotics.[33] One overall result of these differences is that women are 50 to 75 percent more likely than men to experience an adverse drug reaction.[34]

B. Despite These Differences, There is a Long History of Not Including Women in Clinical Trials

Women played a significant role in the development of modern drug testing procedures. With the 1962 Kefauver-Harris Amendment, the FDA began requiring that drugs be proven safe and effective before being introduced to the marketplace.[35] Prior to this, drugs went through only brief experimental phases that were not monitored by the FDA.[36] Drugs could reach the market before researchers had time to examine the results of trials.[37]

The event that sparked the Kefauver-Harris Amendment was the thalidomide epidemic of birth defects.[38] The thalidomide epidemic was in fact

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26. *Id* at 1256.
27. *Id* at 1254.
28. *Id*.
29. *Id*.
30. *Id* (finding that slower renal clearance is particularly problematic for medications that are renally excreted, such as digoxin).
31. *See id.* at 1256-57.
32. *Id.* at 1254.
33. *Id*.
34. *Id*. at 1257.
35. See Bara Fintel et al. *The Thalidomide Tragedy: Lessons for Drug Safety and Regulation*, HELIX (July 28, 2009), https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation [https://perma.cc/9T4L-Y2TZ].
36. *See id*.
37. *See id*.
38. *Id.*

mostly avoided in the United States; the bulk of cases occurred in Germany where the drug had been put on the market without testing.[39] An FDA inspector, Frances Kelsey, had resisted pressure by her supervisors and the drug's manufacturer, and stubbornly held up thalidomide's approval in the U.S.[40] Kelsey was concerned about an insufficient and incomplete body of research surrounding thalidomide; particularly as it might impact fetuses.[41]

Her fears would be validated as doctors in Germany and Australia belatedly realized that a "completely safe" drug that "could not . . . kill a rat" was behind a spate of bizarre and brutal birth defects.[42] Kelsey, by holding up the process, had significantly reduced the number of afflicted mothers and children in the U.S. [43] Because of this, the drug was never released to the mass market, and initial trials had exposed only 20,000 patients to it.[44] This included about 3,760 women of childbearing age, of whom 207 were pregnant.[45] She was viewed as a national heroine.[46] The FDA approval process created by the Kefauver-Harris Amendment turned Kelsey's caution into the law of the land.[47]

Unfortunately, the FDA's new approval process, in its haste to avoid birth defects, took the tack of encouraging researchers to largely exclude women of childbearing age from the drug trial process at all.[48] In 1974, Congress passed the National Research Act, which created the National Commission for the Protection of Human Subjects of Biomedical and Behavorial Research.[49] Five years later, this Commission published the Belmont Report outlining ethical principles concerning human subject research.[50] One of the report's stated principles called for treating pregnant women as vulnerable test subjects.[51]

In the 1980s, this was challenged when a federal task force found that the exclusion of women from studies was impacting understanding of how women reacted to certain drugs.[52] In 1986, the National Institute of Health recommended requiring women to be included in NIH-funded studies unless researchers could provide a valid reason to exclude them.[53] In 1993, Congress

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39. *Id*.
40. *Id*.
41. *Id*.
42. *Id*.
43. *Id.*
44. *Id*.
45. *Id*.
46. *Id.*
47. *Id*.
48. Katherine A. Liu & Natalie A. Dipietro Mager, *Women's Involvement in Clinical Trials: Historical Perspective and Future Implications*, 14 PHARMACY PRAC. 1, 2 (2016).
49. Karen J. Schwenzer, *Protecting Vulnerable Subjects in Clinical Research: Children, Pregnant Women, Prisoners, and Employees*, 53 RESPIRATORY CARE 1342, 1343 (2008).
50. NAT'L COMMISSION FOR THE PROTECTION OF HUM. SUBJECTS OF BIOMEDICAL AND BEHAV. RES., THE BELMONT REPORT (1979).
51. Schwenzer, *supra* note 49, at 1343.
52. *Id*. at 2.
53. *Id*. at 3.

decided to follow this recommendation.[54] In the same year, facing pressure from researchers and women's health advocates, the FDA reversed the 1977 guidelines.[55]

C. There Are Economic and Practical Incentives for Under-Inclusion of Women in Drug Testing

Even after the FDA changed its policy, a problem loomed: studies on women are more difficult than studies on men. Women in clinical trials potentially increase the number of variables for which researchers must account. While both sexes experience hormonal cycles, women's are more dramatic and lead to researcher concern over these cycles creating 'noise' that complicates data collection.[56] Women's hormonal cycles may, of course, impact how drugs work within the body – but from a researcher's standpoint, the cycles can come off as frustrating 'methodological problems.'[57]

Moreover, researchers worry about negative impacts on female participants' fertility (or, worse, birth defects).[58] The concern is certainly not irrational, as many drugs *can* cause birth defects. Sometimes this threat exists even for the most seemingly benign substances. For example, Willow bark-derived aspirin, which humans have used for at least 2,400 years for a variety of ailments,[59] can put women at risk of miscarrying, bleeding internally, and having a child born with asthma.[60]

However, the concern causes research on female subjects to take on paternalistic overtones.[61] Women trial participants have to sign consent forms much more frequently than men, and the wording on consent forms and

54. *Id*.

55. *See id*.

56. *See* Meaghan Callaghan, *Women Are Being Excluded From Clinical Trials*, POPULAR SCIENCE (June 8, 2016) http://www.popsci.com/surprise-researchers-think-women-are-being-excluded-from-clinical-trials **[**https://perma.cc/5LN9-NEZT**]**.

57. LONDA SCHIEBINGER, HAS FEMINISM CHANGED SCIENCE? 114 (1999).

58. Committee on Ethics, American College of Obstetricians and Gynecoloists, *Ethical considerations for including women as research participants, Opinion No. 646* (Nov. 2015), https://www.acog.org/-/media/Committee-Opinions/Committee-on-Ethics/co646.pdf?dmc=1&ts=20180518T0236012290.

59. ALAN JONES, CHEMISTRY: AN INTRODUCTION FOR MEDICAL AND HEALTH SCIENCES 5–6 (2005).

60. Anna Magee, *Everything You Need to Know About Aspirin and Health*, THE TELEGRAPH (Nov. 2, 2015), https://www.telegraph.co.uk/health-fitness/body/health-aspirin-pills-advice-anna-magee-stroke-cancer-prevention-heart-attack/ [perma.cc/5U7U-RJKW].

61. For example, some consent documents warn against pregnancy without giving the woman any information to let her weigh the risks and benefits of the particular medication or procedure to reproductive or fetal health. *See* Marie T. Nolan et al., *Consent Documents, Reproductive Issues, and the Inclusion of Women in Clinical Trials*, 74 ACAD. MED. 275, 275, 278-279 (1999).

multiple signature requirements suggests they are less trustworthy.[62] Although male fertility can also be potentially impacted, men receive far less attention during the consent phase and face weaker language in the forms.[63] Even if a woman does not intend to have children anyway, making future defects irrelevant, many researchers may still take an attitude that it is still not worth the potential liability.[64] Birth control requirements are often out of proportion with the actual risk to a potential fetus.[65] Additionally, even if researchers trusted their female participants to know their own minds and accept their own risks, this creates an inherently self-selecting group. If women are made fully aware of the possible dangers of experimental drugs to future offspring, women who plan on future childbearing may be less likely to participate.

If the scientific challenges were not enough, researchers also must contend with socioeconomic challenges if they wish to include women in their studies. Women may be deterred from participating in clinical trials due to family responsibilities, such as child or eldercare.[66] Women are also more likely than men to work part-time and not have insurance provided via their employer.[67] This is a problem for clinical trials because lack of health insurance is a disincentivize to participating in medical studies.[68]

Finally, it is seen as less pressing. Although women use pharmaceuticals at a greater rate than men, researchers have argued, not infrequently, that performing research mostly on men is nevertheless acceptable, and many researchers will justify not performing biomedical trials on women on the logic that women's longer average lifespans mean they need less medical research. [6970] In other words, the argument is that the impact of exclusion on women cannot be that serious – after all, they still generally outlive men.

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62. Joanna Cain et al., *Contraceptive Requirements for Clinical Research*, 95 OBSTETRICS & GYNECOLOGY 861, 864-65 (2000).

63. *Id*. at 864.

64. *See* R. Alta Charo, *Protecting Us to Death: Women, Pregnancy, and Clinical Research Trials*, 38 ST. LOUIS U. L.J. 135, 168 (1993).

65. Schiebinger, *supra* note 57 at 4.

66. *See* Sara Wilcox et al., *Promoting Adherence and Retention to Clinical Trials in Special Populations: A Women's Health Initiative Workshop,* 22 CONTROLLED CLINICAL TRIALS 279, 285 (2001).

67. Jessica Arons & Lindsay Rosenthal, *The Health Insurance Compensation Gap*, CENTER FOR AMERICAN PROGRESS (Apr. 16, 2012, 9:00 AM), https://www.americanprogress.org/issues/women/reports/2012/04/16/11429/the-health-insurance-compensation-gap/ [https://perma.cc/VY5A-RL6Q].

68. Lisa Schlager, *Insurance Coverage for Clinical Trial Participation: Significant Barriers Remain*, FORCE – FACING OUR RISK OF CANCER, (Sept. 19, 2017), http://www.facingourrisk.org/get-involved/HBOC-community/BRCA-HBOC-blogs/FORCE/advocacy/insurance-coverage-clinical-trials/ [https://perma.cc/GTJ6-GQQK] (stating that the Affordable Care Act addressed part of this problem: under the ACA, insurers cannot discriminate against expenses incurred in clinical trials).

69. *See* Marianne N. Prout & Susan S. Fish, *Participation of Women in Clinical Trials of Drug Therapies: A Context for the Controversies*, MEDSCAPE, https://www.medscape.com/viewarticle/408956_4 [https://perma.cc/4J23-R4YN].

D. The Consequences of Not Including Women in Drug Studies Can Be Severe

If a drug makes it to the general market without adequate testing on women, catching any sex-specific problems may take years. Outside of the closed environment of the scientific study, negative reactions can be extremely difficult to diagnose. Consider, by way of example, the matter of zolpidem.

Zolpidem, best known under the trademark Ambien, is a sedative used to treating insomnia.[71] Women are more likely to suffer from insomnia than men: menstrual hormonal cycles, pregnancy, and menopause all contribute to the greater discrepancy between genders.[72] Women are also more likely to suffer from insomnia-inducing ailments like depression, anxiety, fibromyalgia, and other sleep disorders.[73] Thus, it would logically make sense to be especially concerned about how women react to sleep medications. Instead, zolpidem was on the market for nearly 20 years before the FDA officially recognized that men and women react very differently.[74]

The drug was released to the market in 1993, prior to the FDA lifting the ban on childbearing-aged women participating in most clinical drug trials.[75] The FDA did not take steps to adjust the female zolpidem dosage until almost twenty years later.[76] However, women did not begin to react poorly to zolpidem

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70. Jeff Hansen, *Why Do Women Live Longer than Men?,* PHYS.ORG (June 14, 2016), https://phys.org/news/2016-06-women-longer-men.html [https://perma.cc/KC2F-9DF2] (explaining that it is worth noting that we still do not quite know *why* women so routinely outlive men—and more remarkably, do so even though women on average have more health problems. Around 90 percent of supercentenarians (those 110 years or older) are female. Estrogen, most commonly cited as the reason, can account for only some of the difference).

71. *Questions and Answers: Risk Of Next-Morning Impairment After Use of Insomnia Drugs; FDA Requires Lower Recommended Doses for Certain Drugs Containing Zolpidem (Ambien, Ambien CR, Edluar, And Zolpimist),* U.S. FOOD & DRUG ADMINISTRATION, https://www.fda.gov/drugs/drugsafety/ucm334041.htm [https://perma.cc/H2QN-ACXE].

72. *Insomnia Fact Sheet*, WOMENSHEALTH.GOV, https://www.womenshealth.gov/publications/our-publications/fact-sheet/insomnia.html#c [https://perma.cc/64LP-3T55] (last visited Mar. 18, 2018).

73. *Id*.

74. *Questions and Answers: Risk of Next-morning Impairment After Use of Insomnia Drugs; FDA Requires Lower Recommended Doses for Certain Drugs Containing Zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)*, FOOD AND DRUG ADMIN., Question 7, http://www.fda.gov/drugs/drugsafety/ucm334041.htm [https://perma.cc/X534-ZFVL] (last updated Feb. 13, 2018).

75. Katherine A. Liu & Natalie A. Dipietro Mager, *Women's Involvement in Clinical Trials: Historical Perspective and Future Implications*, PHARMACY PRACTICE, Feb. 16, 2016, at 1, 3; Department of Health and Human Services, 58 Fed. Reg. 39406 (July 22, 1993).

76. *FDA Drug Safety Communication: FDA Approves New Label Changes and Dosing for Zolpidem Products and a Recommendation to Avoid Driving the Day After Using Ambien CR*., FOOD AND DRUG ADMIN., https://www.fda.gov/drugs/drugsafety/ucm352085.htm [https://perma.cc/2XYW-8D4W] (last updated Dec. 11, 2017).

in the 2010s: what happened in the 2010s was the FDA officially recognizing a long-standing problem.

Why do women react differently to zolpidem? Quite simply, because women have higher percentages of body fat, they eliminate fat-solvable drugs like zolpidem from their bodies more slowly than men do.[77] The result can be explained as, if a woman takes 10 mg of zolpidem at 5 pm will she have more lingering in her system at 8 am the next morning than a man would if he took the same dosage. The safe dosage for women appears to be about half the male dosage – women are now to take 5 mg for immediate-release drugs (instead of 10 mg) and 6.25 mg for long-term release (instead of 12.5 mg.)[78] This would likely have been discovered before the drug's release, had it been properly tested on women.

Zolpidem has other rarer side effects that increase in likelihood with an overdose (which, again, many women were effectively experiencing every time they took the drug.). The most serious is a drug-induced amnesia. People have reported eating, driving, walking, making phone calls, or having sex, and then not remembering it afterward. [79] This has made zolpidem a popular date rape drug.[80]

People acting under the stranger side effects of zolpidem might be presumed drunk, drugged, or very tired. People who were pulled over doing something illegal (e.g. driving) might not be able to provide useful information about the incident. While zolpidem was being caught in blood screening in the 1990s, it was often impossible to say with certainty how long it took for the effect to have a physical manifestation: in other words, just how much time had elapsed between taking the pill and being pulled over for erratic driving.[81] Zolpidem has a history of being an alleged cause of parasomnia in criminal or civil cases, raising questions about the defendant's *mens rea*.[82]

Consider a North Carolina case with an arch-typical Ambien-overdose story, *State v. Wright*.[83] The *Wright* defendant drove her car into a utility pole

77. *See* FOOD AND DRUG ADMIN., *supra* note 71, at Introduction.

78. *Zolpidem Dosage*, DRUGS.COM, https://www.drugs.com/dosage/zolpidem.html [https://www.drugs.com/dosage/zolpidem.html] (last visited Mar. 18, 2018).

79. *Ambien*, DRUGS.COM, https://www.drugs.com/ambien.html [https://perma.cc/H3CB-AGQK] (last updated Mar. 5, 2017, 9:30 AM).

80. Brent Schrotenboer, *Darren Sharper Case Spotlights Sleep Drug's Dark Side*, USA TODAY SPORTS (Mar. 26, 2014, 11:22 PM), http://www.usatoday.com/story/sports/nfl/2014/03/26/darren-sharper-ambien-zolpidem-insomnia-date-rape-case/6930621/ [https://perma.cc/R764-5BXR] (explaining that after Rohypnol (of the term "roofie") was outlawed in 1996, various zolpidem brands have taken its place as the date rape drug of choice).

81. Barry K. Logan & Fiona J. Couper, *Zolpidem and Driving Impairment*, 46 J. OF FORENSIC SCI. 105, 109 (2001).

82. Naren Gunja, *In the Zzz Zone: The Effects of Z-Drugs on Human Performance and Driving*, 9 J. OF MED.TOXICOLOGY 163, 168 (2013).

83. State v. Wright, 204 N.C. App. 212, 694 S.E.2d 522 (Table), 2010 WL 1960803 (unpublished).

while under the drug's influence.[84] She had no memory of the events of the crash.[85] She did not deny that the person in the videotape was herself; however, she had no memory of saying any of the things that she said.[86] The dosage Wright took is not reported in the record to have been extreme, but it was enough to give her amnesia about the entire incident.

Additionally, a sleep drug might have symptoms that even the patient regularly overdosing might not realize are symptoms. If a woman is accustomed to being drowsy in the morning, as many people are, she might very reasonably not realize that the reason she is so sleepy at seven am is because she is still under the effects of a sleeping pill. Thus, doctors could not rely on patient reports of side effects to flag zolpidem's ill effects.

After almost two decades of reports about the dangerous side effects from zolpidem, the FDA finally took the step of "black boxing" it – putting a warning on it, and advising physicians to reduce the female dosage by half.[87] While a step in the right direction, this was a little too late for all the women who suffered ill effects over the years simply for following doctors' instructions. Nor do we know what the next zolpidem will be – only that zolpidem is certainly not the only drug on the market where women are left to suffer side effects for lack of proper research.

III. IT IS IN THE GOVERNMENT'S INTERESTS TO MANDATE THAT DRUG TRIALS TAKE INTO ACCOUNT PATIENT DEMOGRAPHICS

Consider an alternate universe where women were included in the zolpidem drug trials from the start. In a controlled study over a long period of time, it would have been far more likely that researchers would have spotted that the drug has stronger effects on women than men. Had researchers known from early in the process that women react differently, researchers could have headed the problem off at the pass: the female dosage could have *always* been half the male dosage.

Zolpidem is unlikely to be the only drug with lingering ramifications from past exclusion of women in clinical drug trials. Consider the following short illustrations of areas where past exclusion and present under-representation may have lingering impacts.

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84. *Id*. at *1.

85. *Id*. at *3.

86. *Id*.

87. *FDA Drug Safety Communication: FDA Approves New Label Changes and Dosing for Zolpidem Products and a Recommendation to Avoid Driving the Day After Using Ambien CR*., FOOD AND DRUG ADMIN., https://www.fda.gov/drugs/drugsafety/ucm352085.htm [https://perma.cc/2XYW-8D4W] (last updated Dec. 11, 2017).

A. Requiring Drug Researchers to Fully Include Women in Clinical Trials May Help Stem the Tide of Prescription Drug Abuse

Women are more likely than men to be addicted to prescription drugs, especially painkillers.[88] Unlike men, women who abuse prescription drugs often do so within the context of treating a medical ailment, not recreational use.[89] They are also more likely to fatally overdose.[90] In 2010, over 6,600 women died from prescription overdoses, a 400% jump from 11 years prior.[91]

Many—possibly most—of these women did not set out to intentionally abuse their medications. Women are more likely than men to go to the doctor; suffer from chronic pain; be prescribed medication; and tend to receive higher doses for longer periods than men.[92] None of this indicates intent by either women or their physicians to overuse prescription drugs. If women go to the doctor more than men and complain of pain more than men, women will tend to receive more prescriptions for painkillers.

However, women being routinely given higher doses of opiates than men should raise alarm bells—because women's bodies are more sensitive to opiates than men's.[93] Women's bodies begin to react to opiates faster than men's, and the drugs remain active in a woman's system for longer.[94] This would suggest that, as with zolpidem, we might reasonably expect women to be given *smaller* doses. Yet we do not—because women are the 'squeaky wheel'.

If opiates were non-addictive, this might be chalked up as 'counterintuitive, but harmless.' However, opiates are highly addictive.[95] Worse, evidence suggests that women's bodies are naturally more vulnerable to drug dependencies than men's.[96] Well-intentioned physicians may be unaware of this increased vulnerability. Sex-based testing on opiates has been very much an afterthought.[97] [98]

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88. Harvard Mental Health Letter, *Addiction in Women*, HARV. HEALTH PUB. (Jan. 2010), www.health.harvard.edu/newsletters/Harvard_Mental_Health_Letter/2010/January/addiction-in-women [https://perma.cc/7A3M-QM55].

89. *Id*.

90. *Prescription Painkillers Are Claiming More Women's Lives*, NAT'L INST. ON DRUG ABUSE (July 26, 2013), https://www.drugabuse.gov/about-nida/noras-blog/2013/07/prescription-painkillers-are-claiming-more-womens-lives [https://perma.cc/S997-7VET].

91. *Id.*

92. *Id*.

93. Whitley & Lindsey, *supra* note 25, at 1255.

94. *See Id*.

95. *See Help, Resources and Information National Opioids Crisis,* U.S. DEP'T OF HEALTH AND HUM. SERVS., https://www.hhs.gov/opioids/ [https://perma.cc/K6SS-9V3V] (last visited Mar. 18, 2018).

96. See NAT'L INST. ON DRUG ABUSE, *supra* note 87; *see also* Whitley & Lindsey, *supra* note 25, at 1257.

97. Jeanne Manubay et al., *Sex Differences Among Opioid-Abusing Patients With Chronic Pain in a Clinical Trial*, 9 J. ADDICTION MED. 46, 46-52 (2015).

As an aside, resources for women with opiate addictions often focus heavily on potential pregnancy complications. To be fair, opiate abuse is severely dangerous to fetal health—and, to be charitable, drug rehab advocates may be reasonably assuming that a woman's concern for her child is extra motivation to get clean. Nevertheless, it suggests that the old presumption that a woman's first priority, outweighing her own health, is a healthy child—the same presumption that kept women out of drug trials for decades—is still going strong.

Nearly half of Americans know at least one person with an opioid addiction.[99] In polls, sixty percent wanted Congress to take more action to halt it.[100] Mandating female participation in drug trials would be a helpful step in the right direction to head off similar results in the future. If a pharmaceutical has stronger and more addictive qualities for women, women and their physicians ought to know from the outset, not decades later.

None of this is to suggest that women should be discouraged from seeking painkillers, or denied help for serious pain out of addiction fears. But if a woman goes to her physician with chronic pain, she and her doctor should be able to have a serious and respectful conversation about how much she can safely take, how long she can safely take it, and what warning signs she can look out for. If drug researchers take a closer look at potential hazards for women before future painkillers hit the marketplace, it will be easier for patients to take proactive steps to keep themselves from becoming addicted.

B. Mandatory Female Inclusion in Drug Trials Will Allow the Health Care Industry to Better Treat Major Killers, Like Heart Disease

Heart disease is one of the U.S.'s deadliest killers. One in four American women will die from heart disease.[101] Some of this has nothing to do with treatment and everything to do with statistics. Heart disease is heavily

98. *See* Hendree E. Jones, et al., *Treatment of Opioid Dependent Pregnant Women: Clinical and Research Issues*, 35 J. SUBSTANCE ABUSE TREATMENT 245, 246 (2008), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2633026/pdf/nihms71150.pdf [https://perma.cc/7NTU-8FWY];
see also FAQ: Opiates and Pregnancy, CRC HEALTH GRP., http://www.crchealth.com/addiction/heroin-addiction-treatment/heroin-detox/opiates_pregnancy [https://perma.cc/XYQ7-5KT9](last visited Mar. 8, 2018).

99. Tom Howell, Jr., *Congress Must Do More to Fight Opioid Crisis: Poll*, WASH. TIMES (May 3, 2016), https://www.washingtontimes.com/news/2016/may/3/congress-must-do-more-to-fight-opioid-crisis-poll/ [https://perma.cc/YL5S-WY7Z].

100. *Id.*

101. *Heart Disease in Women*, NAT'L HEART, LUNG, & BLOOD INST., https://www.nhlbi.nih.gov/health/health-topics/topics/hdw [https://perma.cc/734D-DGSR](click "How Does Heart Disease Affect Women?" link) (last visited Mar. 9, 2016).

correlated with age.[102] Because of the longer average female lifespan, this threat can loom large.

However, as noted previously, some of the threat to women comes from physical differences with men. There are two types of heart disease which largerly affect women, coronary microvascular disease (MVD) and broken heart syndrome.[103] These heart diseases are less well-understood than coronary heart disease, which affects both genders.[104] MVD may be missed by physicians who expect to see damage to the main arteries or the heart itself. This damage is what is commonly expected in men with heart disease. The expectation might cause doctors to not look at the network of smaller blood vessels in or around the heart, which is where the damage occurs in MVD.[105] In addition, because estrogen has insulating qualities, women develop heart disease an average of a decade later than men.[106] There are subtler differences between the female and male cardiovascular system, including differences in coronary function and blood pressure.[107]

Although research into female heart disease has increased in recent years, women continue to be sidelined in clinical drug trials for heart disease treatments. In 2007, women were only involved in 41% of clinic trials regarding cardivascolar disease.[108] The lack of women in these trials is more peculiar when one remembers that researchers cite fertility and birth defect

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102. The American Heart Association's 2015 numbers place coronary heart disease's prevalence at 32.2% for men 80+ and 18.8% for women of the same age group. *Older Americans & Cardiovascular Disease*, AM. HEART ASS'N (2015), https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_472923.pdf [https://perma.cc/U9FX-R5TX].

103. Also called, less poetically, "Takotsubo Cardiomyopathy." Broken heart disease is exactly what you might expect: a temporary heart condition brought on by heavy stress, e.g., a bad breakup, dead relative, serious illness, etc. *See,* NAT'L HEART, LUNG, & BLOOD INST., *supra* note 101; *see generally Broken Heart Syndrome*, MAYO CLINIC, (Nov. 5, 2016) http://www.mayoclinic.org/diseases-conditions/broken-heart-syndrome/home/ovc-20264165 [https://perma.cc/DNY3-3QXY].

104. *See,* NAT'L HEART, LUNG, & BLOOD INST., *supra* note 101.

105. *See Heart Attack and Stroke: Men vs. Women*, HARV. HEALTH PUB.: HARV. HEALTH LETTER (Apr. 2014), https://www.health.harvard.edu/heart-health/heart-attack-and-stroke-men-vs-women [https://perma.cc/C29F-WNQ9].

106. A.H.E.M. Mass & Y.E.A. Appelman, *Gender Differences in Coronary Heart Disease*, 18 NETH. HEART J. 598, 598 (Dec. 2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3018605/pdf/nhj1859800.pdf [https://perma.cc/223D-7VZK].

107. *See* Virginia H. Huxley, *Sex and The Cardiovascular System: The Intriguing Tale of How Women and Men Regulate Cardiovascular Function Differently*, 31 ADVANCES IN PSYCHOLOGY AND EDUC. 17, 17 (Nov. 28, 2006), https://www.physiology.org/doi/pdf/10.1152/advan.00099.2006 [https://perma.cc/MWX3-89HM].

108. Chiara Melloni, et al., *Representation of Women in Randomized Clinical Trials of Cardiovascular Disease Prevention*, AM. HEART ASSOC., Feb. 16, 2010, at 1, http://circoutcomes.ahajournals.org/content/circcvoq/early/2010/02/16/CIRCOUTCOMES.110.868307.full.pdf [https://perma.cc/24BG-WPPG].

concerns as a major objection to inclusion, because women rarely display signs of heart disease until after menopause.[109]

A lack of proper research inhibits our ability to take preventive steps—and that costs the taxpayer. In 2012, the direct costs of heart failure were estimated at $20.9 billion for a single year's worth of treatments and hospitalizations.[110] By 2030, this is expected to more than double, to $53.1 billion a year.[111] An aging population means more health care costs—money that will be disproportionately spent on women, simply because women live longer than men. It would thus be objectively in the government's interest to help those women manage heart disease with safe and effective medications, rather than spend the money on hospital beds and lifesaving procedures.

Better inclusion of women in clinical drug trials may also increase awareness of the threat heart disease poses to women. While women are generally more aware of and involved in their health care than men,[112] heart disease is an exception.[113] Women tend to wait longer to seek treatment for heart disease than men .[114] While recent research has called into question the belief that women usually have 'atypical' heart attack symptoms,[115] women's heart attacks can feature symptoms other than chest pain.[116] Women also appear much more likely to have 'silent' heart attacks, or heart attacks in their sleep.[117] Because women are more likely to experience heart disease when they are older and more physically fragile, and because women's heart attacks are more likely to be 'silent,' women need to be encouraged to get ahead of the problem.

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109. Menopause does not cause heart disease, but the natural drop in estrogen takes away much of the female body's resistance. *See Menopause and Heart Disease*, AM. HEART ASSOC., http://www.heart.org/HEARTORG/Conditions/More/MyHeartandStrokeNews/Menopause-and-Heart-Disease_UCM_448432_Article.jsp#.WqwlNZPwZAZ [https://perma.cc/RFX4-MLFW](last updated June 23, 2017).

110. Kathryn Fitch, et al., *The High Cost of Heart Failure for the Medicare Popluation: An Actuarial Cost Analysis*, MILLIMAN, Feb. 2015, at 1, http://us.milliman.com/uploadedFiles/insight/2015/heart-failure-cost-medicare-analysis.pdf [https://perma.cc/88ZB-WLJW].

111. *Id.*

112. *See See* Loyola U. Health Syst., *National Survey Finds Women More Likely To See Doctor On Regular Basis Than Men*, NEWS-MEDICAL.NET (June 9, 2011), https://www.news-medical.net/news/20110609/National-survey-finds-women-more-likely-to-see-doctor-on-regular-basis-than-men.aspx [https://perma.cc/77RD-2Z37].

113. *See Heart disease in women: Understand symptoms and risk factors*, MAYO CLINIC (Feb. 23, 2018), https://www.mayoclinic.org/diseases-conditions/heart-disease/in-depth/heart-disease/art-20046167 [https://perma.cc/E3LL-SV2J].

114. *See The Heart Attack Gender Gap*, HARV. HEALTH LETTER: HARV. HEALTH PUB. (Apr. 2016), https://www.health.harvard.edu/heart-health/the-heart-attack-gender-gap [https://perma.cc/GG8E-KKEC].

115. *Heart Attack amd Stroke: Men vs. Women*, HARV. HEALTH LETTER: HARV. HEALTH PUB. (Apr. 2014), http://www.health.harvard.edu/heart-health/heart-attack-and-stroke-men-vs-women [https://perma.cc/C29F-WNQ9].

116. *See* MAYO CLINIC, *supra* note 113.

117. *Id*.

Increasing women's participation in clinical drug testing for heart disease medications will help. By including female participants proportional to the expected population that will actually use the drug, researchers will be able to better predict how women will react. Medication is a less expensive and intrusive remedy to heart disease than intrusive surgeries, but many medications must be begun early for best effect.[118]

C. Including a Representative Population of Women in Clinical Drug Trials Will Avoid Embarrassing and Dangerous Incidents

Even if women's exclusion from clinical drug trials had no immediate negative consequences for anyone but individual women, it would be in the government's interests to mandate inclusion. Clinical drug trials and other biomedical research have yielded up a treasure trove of fascinating data about the human body.

While inclusion of women into drug trials may increase the expense of conducting trials and thus slow research, the drugs that will be released onto the market will be able to be used more safely. When policymakers consider this problem, they should not make the same irrational choice that researchers made in the 1970s: they should not ignore the problem and hope for the best when their drug hits the market. Women do not simply abstain from taking prescription drugs because they have been less well-studied.

Further, more careful inclusion of women would spare manufacturers from facing a larger and more embarrassing expense from settlements and negative publicity once word of a drug's dangers hit the general public. Manufacturers who produce zolpidem pills, like Ambien, faced a great number of lawsuits following the FDA's dosage change.[119] It is difficult to know how much manufacturers have actually shelled out to aggrieved zolpidem users, as these lawsuits have generally settled out of court. But between losses from settlements and potential customers scared away by a firestorm of negative press, it is difficult to believe that including women in the initial studies would have been the pricier option.

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118. For example, blood pressure pills taken before the patient has full-blown heart disease may reduce heart attacks and strokes. Howard LeWine, *Taking blood pressure pills at bedtime may prevent more heart attakcs, strokes*, HARV. HEALTH PUB.: HARV. HEALTH BLOG (Oct. 25, 2011), http://www.health.harvard.edu/blog/taking-blood-pressure-pills-at-bedtime-may-prevent-more-heart-attacks-strokes-201110253668 [https://perma.cc/MA6J-APSY]; Michael Bloomquist, *Women and Heart Disease*, WEDMD (May 22, 2000) https://www.webmd.com/heart-disease/guide/women-heart-disease#1 [https://perma.cc/JZS7-KPZ3].

119. *Ambien Lawsuit*, DRUGDANGERS, http://www.drugdangers.com/ambien/lawsuit.htm [https://perma.cc/YL68-FR6E] (last visited Mar. 17, 2018).

IV. S.2745 ("ADVANCING NIH STRATEGIC PLANNING AND REPRESENTATION IN MEDICAL RESEARCH ACT")

In April of 2016, Senators Susan Collins (R-Maine), Elizabeth Warren (D-Mass.), Mark Kirk (R-Ill.), Tammy Baldwin (D-Wis.), Chairman Lamar Alexander (R-Tenn.), and Ranking Member Patty Murray (D-Wash.) introduced the Advancing NIH Strategic Planning and Representation in Medical Research Act.[120]

A. An Overview of S.2745's Purpose

S.2745 was intended to push the National Institutes of Health to diversify their study participants. If passed, it would have required the NIH to develop a six-year plan to start addressing the disparity.[121] In other words, because the issue involves such a technical and complicated issue, its sponsors were not attempting a fix from the Congress per se – instead, they wished to task the relevant agency with figuring out a plan.

The bill's goals were not exclusive to women: the proposed plan was also to increase NIH research involving people of color and LGBT populations. Different ethnic groups have different reactions to certain drugs: e.g., tacrolimus, which is used in organ transplants, is noticeably different in how it impacts white and Latino patients versus how it impacts African American patients.[122] The most recent action was on 09/28/2016, when it was referred to the House Committee on Energy and Commerce. There are 25 lobbyists on record regarding the bill. Most are research groups, including multiple universities. [123]

120. Advancing NIH Strategic Planning and Representation in Medical Research Act, S. 2745, 114th Cong. (as reported to the Senate, Apr. 18, 2016), https://www.congress.gov/bill/114th-congress/senate-bill/2745/text [https://perma.cc/R7SE-9S4B].

121. *See generally id*, including Sec. 3 (1)(B)(i)(1).

122. S.U. Yasada et al., *The Role of Ethnicity in Variability in Response to Drugs: Focus on Clinical Pharmacology Studies*, 84 CLINICAL PHARMACOLOGY & THERAPEUTICS 417, 418 (2008).

123. One of which happens to be the University of Wisconsin. The Center for Responsive Politics, *Clients Lobbying on S.2745: Advancing NIH Strategic Planning and Representation in Medical Research Act*, OPENSECRETS.ORG, https://www.opensecrets.org/lobby/billsum.php?id=s2745-114 [https://perma.cc/3L2V-W77U] (last visited March 13, 2018).

B. The 21st Century Cures Act

S.2745 was introduced as part of a fleet of companion legislation to the 21st Century Cures bill.[124] Congress passed the 21st Century Cures Act in December of 2016.[125] The final Act included elements from several of the companion bills, and enjoyed bipartisan support with a 94 to 5 vote.[126] The final product addressed one demographic concern by asking the NIH to study appropriate age groupings in clinical research.[127] Women's inclusion in that research, however, was not addressed.

If anything, the 21st Century Cures Act greatly reduced the regulatory burden on clinical trials, leading to fierce criticism from patient advocates.[128] One critic in the LA Times characterized the bill as a "huge deregulatory giveaway to the pharmaceutical and medical device industry, papered over by new funding for those research initiatives."[129] The deregulation was certain but the funding was not, because it will be subject to uncertain annual appropriations.[130]

As an example of the proposed deregulation, section 3042 of the bill encourages the FDA to reduce the required trial group for antibiotic research.[131] There is a defensible logic to this decision: specialized antibiotics can be difficult to get onto the market if the bacteria they fight are rare. If a certain bacteria affects only a small number of people a year, available participants for potential research will be limited.[132] But there is a concerning trade-off

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124. Companion bills covered a range of issues from rare pediatric diseases to the transmission of "superbugs" via medical devices. Zachary Brennan, *Senate Committee Advances Five More Bills as Part of Medical Innovation Package*, REGULATORY AFFAIRS PROFESSIONALS SOCIETY (Apr. 6, 2016), https://www.raps.org/regulatory-focus™/news-articles/2016/4/senate-committee-advances-five-more-bills-as-part-of-medical-innovation-package [https://perma.cc/7JCQ-FVHT].

125. Mike DeBonis, *Congress Passes 21st Century Cures Act, Boosting Research and Easing Drug Approvals*, THE WASHINGTON POST (Dec. 7, 2016), https://www.washingtonpost.com/news/powerpost/wp/2016/12/07/congress-passes-21st-century-cures-act-boosting-research-and-easing-drug-approvals/ [https://perma.cc/A7RJ-FHTF].

126. *Id*.

127. 21st Century Cures Act, Pub. L. No.114-255, §2038(h)(2)(C)(i), 130 Stat. 1033 (2016) (West).

128. *See Preventing Patient Harm in 21st Century Cures*, PUBLIC CITIZEN, http://www.citizen.org/documents/concerns-21st-century-cures-november28.pdf [https://perma.cc/2FTF-2YUA] (last visited Mar. 14, 2018).

129. Michael Hiltzik, *The 21st Century Cures Act: A Huge Handout to the Drug Industry Disguised as a Pro-Research Bounty*, THE LOS ANGELES TIMES (Dec. 5, 2016, 3:45 PM), http://www.latimes.com/business/hiltzik/la-fi-hiltzik-21st-century-20161205-story.html [https://perma.cc/XB7X-FF4T].

130. *Id*.

131. 21st Century Cures Act, Pub. L. No.114-255, §3042, 130 Stat. 1033 (2016) (West).

132. *See generally* Chris Dall, *Health Groups Urge Senate to Pass Antibiotics Bill*, CENTER FOR INFECTIOUS DISEASE RESEARCH AND POLICY (Sept. 6, 2016),

involved: small sample sizes makes it harder to have representative demographics in these studies. If the test group ends up being largely male, this opens up potential problems for women patients, as women have been known to react differently to some antibiotics.[133]

V. S.2745'S CHANCE OF PASSAGE IN THE CURRENT POLITICAL ENVIRONMENT IS LIKELY MINIMAL

Unfortunately for S.2745's drafters, the current political climate is unlikely to be favorable. It is still possible that the bill, or something similar, may eventually come to the floor and be passed—but clinical trial reform will need to navigate a thorny set of problems first.

A. The Current Political Climate is Generally Hostile to New and Stricter Regulation

While it is too early to say for certain how the Trump Administration feels about women and clinical trials, President Trump has made it clear that he is generally opposed to a heavy regulatory burden. His sentiments were made abundantly clear on the campaign trail, when he frequently promised to slash regulation. As President-elect, he issued a statement promising to "formulate a rule which says that for every new regulation, two old regulations must be eliminated."[134]

Current FDA Commissioner Scott Gottlieb is a prominent proponent of studying medications via real-world evidence, or RWE.[135] The term encompasses a broad range of "many different forms of information derived from sources generally outside of randomized, controlled clinical trials . . . includ[ing] electronic health record (EHR) data, claims and billing data, product and disease registries, and data from personal devices or health applications."[136] It is data gathered on the ground, from marketplace use of

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http://www.cidrap.umn.edu/news-perspective/2016/09/health-groups-urge-senate-pass-antibiotics-bill [https://perma.cc/TJ85-ZYSC].

133. For example, antibiotics like tetracycline (used for treating a broad spectrum of bacteria) require an empty stomach for proper absorption; slower female metabolisms can pose problems. Tammy Worth, *Drugs that Work Differently in Men and Women*, EVERYDAY HEALTH, http://www.everydayhealth.com/news/drugs-work-differently-woman-than-man/ [(last updated Feb. 19, 2015).

134. Crews, *supra* note 17.

135. Michael Causey, *FDA's Gottlieb Pushes Use of Real-World Evidence in Clinical Trials*, ASS'N OF CLINICAL RESEARCH PROFESSIONALS: BLOG (Sept. 21, 2017), https://www.acrpnet.org/2017/09/21/fdas-gottlieb-pushes-use-real-world-evidence-clinical-trials/ [https://perma.cc/2V9H-7638].

136. Zachary Brennan, *FDA Says Real-World Evidence Could Generate "Incorrect or Unreliable Conclusions*", REGULATORY AFFAIRS PROFESSIONALS SOC'Y (Dec. 8, 2016),

medical treatments. An FDA analysis of RWE was mandated by the 21st Century Cures Act.[137]

The FDA has previously expressed serious qualms with RWE. While it can be a valuable source, RWE is also haphazard by nature. In a clinical trial, data is collected in a controlled environment, with the goal of supporting research. As an FDA study pointed out:

EHR and claims data are not collected or organized with the goal of supporting research, nor have they typically been optimized for such purposes, and the accuracy and reliability of data gathered by many personal devices and health-related apps are unknown . . . the use of any of these sources, including social media, raises important questions about the quality of the data they provide and about privacy.[138]

This is potentially troubling if the expected or observed effect of a treatment is relatively small: it becomes nearly impossible to separate correlation and causation, already challenging even in a controlled clinical environment.[139]

Arguably, an increased reliance on RWE would be more of the same for women. Recall again our zolpidem example: because women's reactions were not properly studied, doctors learned what it does to the female body after the drug was already in widespread use. And this pinpoints the problem with RWE. Because real world patients exist outside a controlled environment and a drug side effect can be easily mistaken for something less serious (see: zolpidem and doctors mistaking overdoses for regular drowsiness), dangerous reactions can go a very long time before being formally addressed.

Changes in technology may make RWE more reliable. Zolpidem hit the marketplace when the medical field was barely beginning to digitalize. Although EHR software has existed in some form since 1972, hospitals were slow to adopt it due to the expense and laborious retraining required.[140] As late as 2008, one study found that only twenty percent of hospitals and five percent of clinics were using EHR, mostly due to the prohibitive cost.[141] However, the

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https://www.raps.org/regulatory-focus™/news-articles/2016/12/fda-says-real-world-evidence-could-generate-incorrect-or-unreliable-conclusions' [https://perma.cc/5WKW-C3LJ].

137. 21st Century Cures Act, Pub. L. No.114-255, §3022, 130 Stat. 1033 (2016) (West).

138. Brennan, *supra* note 136.

139. *See Id*.

140. Venkataraman Palabindala et al., *Adoption of Electronic Health Records and Barriers*, J. COMTY HOSP. INTERNAL MED. PERSPECTIVES (Oct. 26, 2016), https://www.tandfonline.com/doi/pdf/10.3402/jchimp.v6.32643?needAccess=true [https://perma.cc/Q2SJ-EA9D].

141. *See generally* JaWanna Henry et al., *Adoption of Electronic Health Record Systems Among U.S. Non-Federal Acute Care Hospitals: 2008-2015*, HEALTH IT (May, 2016), https://dashboard.healthit.gov/evaluations/data-briefs/non-federal-acute-care-hospital-ehr-adoption-2008-2015.php [https://perma.cc/3LVV-FFMM].

software industry has since produced a much wider—and cheaper—range of EHR options, greatly increasing usage.[142]

A regulatory rollback may also make it harder for small, innovative companies to compete. In a marketplace where companies will only need to prove their product 'safe' before taking it to the market, pharmaceutical giants like Pfizer will have a distinct competitive advantage. Biotech entrepreneurs have expressed concerns that their own companies will be pushed out of the market.[143] The FDA's current safety and efficiency requirements allow small companies to race the giants for approval: if a small company and a large one both develop a drug that meets the minimum safety requirements, but the small company's product is more efficient, the small company can be approved first and corner the market.[144]

With efficacy dropped from the preliminary trials and tested on the general market, releasing a new medication to the market would primarily be a question of simply proving that it will not kill its users (at least not right away). Recall that clinical trials must juggle more complex factors if women are included in them.[145] Should the current FDA approval process be rolled back, researchers will be incentivized to include women less, not more.

VI. CONCLUSION

Women respond differently than men to many medications: this is an indisputable fact, known for decades. Despite this knowledge, and despite a pharmaceutical market that serves more women than men, women continue to be routinely excluded from early clinical trials. If they are included, it is towards the end of testing. This continues to allow gender differences to slip past researchers until the drug hits the market.

This article has explored the reasons for this gender gap. A customary presumption that white men were a universal baseline turned into a formal prohibition, driven by an understandable but ill-considered fear. When the FDA finally reversed itself, a research bias persisted. Even with knowledge that women patients may be endangered if women are excluded from drug trials, economic and cultural factors discourage inclusion.

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142. There are hundreds of varieties of EHR on the marketplace; Wisconsin readers may be particularly familiar with EPIC. Most EHR software is programmed to flag and warn physicians of at least some demographic-based risks when prescribing drugs. *Electronic Medical Records Software*, SOFTWARE ADVICE, http://www.softwareadvice.com/medical/electronic-medical-record-software-comparison/#buyers-guide [https://perma.cc/87PN-PE4K] (last visited Mar. 15, 2018).

143. *See generally* Matthew Herper, *Why Donald Trump's Punative FDA Pick Could Scare Pharma*, FORBES (Dec. 8, 2016, 10:03 AM), http://www.forbes.com/sites/matthewherper/2016/12/08/why-donald-trumps-putative-fda-pick-could-scare-pharma/#4eb44d8058a4.

144. *Id*.

145. Callaghan*, supra* note 56.

Because this bias has persisted, I have argued for a flat ban on market release of any drug that has not been tested on its expected usage demographics. This would mean that any drug that will be used by an equal number of men and women ought to be tested on an equal number of men and women. This policy may help combat opioid addiction in women, decrease medical expenses from heart disease in old age, and ward off another zolpidem-style health crisis.

Unfortunately, the regulatory trend appears to be moving in the opposite direction. The proposed S.2745 is essentially dead in the water unlikely to move past its subcommittee, while the 21st Century Cures Act aimed to reduce the regulatory burden without addressing women's concerns at all. The new administration appears generally hostile to regulation, and the push for a greater use of RWD is—though not necessarily bad in and of itself—a remedy that does not necessarily address subtler side effects. Clinical trials take longer when women are represented, and the new emphasis is on speed—which makes solving the clinical trial gender gap unlikely at best.

It seems unlikely that clinical drug trials will be conducted on realistic demographics anytime soon. Nevertheless, I believe the issue will—eventually—have to be addressed. The routine exclusion of women from trials is dangerous. It is also scientifically unsound, and fundamentally unjust.