Fewer than 1% of United States clinical drug trials enroll pregnant participants

OBJECTIVE: Although there has been advocacy to increase pregnant representation in research including randomized clinical trials (RCTs),[1] there is a lack of systematic information about the frequency and types of RCTs that enroll pregnant participants. We use data from ClinicalTrials.gov to comprehensively quantify the proportion, characteristics, and funding of RCTs open to women of 18 to 45 that have enrolled pregnant people over the past 15 years, characterizing gaps in evidence related to drug safety and efficacy during pregnancy.

STUDY DESIGN: We analyzed data for all drug RCTs posted from 2008 to 2023, compiled in the Aggregate Analysis of Clinical Trials database,[2] extracting fields for title, status, age, gender, type, masking, and funding sources as well as free text fields for summary, inclusion/exclusion criteria, and conditions. We first limited our sample based on gender (included females), age (included individuals 18−45), status (not Withdrawn prior to enrollment or Unknown), and location/funding (US location, US government-funded, or industry-funded). We chose location/funding criteria to limit trials that were likely required to register on the website: beginning December 2007, US regulations mandated that all "controlled clinical investigations" of post-Phase 1, US Food and Drug Administration-regulated drug interventions register on ClinicalTrials.gov, and registration later became required for National Institutes of Health-funded studies.[3−5]

Using title, summary, and inclusion criteria, we categorized each RCT based on whether it included, excluded, or did not explicitly mention pregnant participants, with the latter encompassing all RCTs in which inclusion criteria did not mention pregnancy, even when inclusion was unlikely (eg, chemotherapy studies). We marked RCTs with interventions provided only in the postpartum period as well as those related to abortion or treatment of fetal demise as "excluded," thereby limiting RCTs "including" pregnant participants to those in which there was an anticipated live birth.

Classifications were generated first using GPT-4o after evaluating performance on a human-labeled training set (1.5% misclassification rate) with validation on a separate human-labeled dataset (1.8% misclassification rate, ≥98% predictive value in each class [included/excluded/unspecified]). For a random sample of 50 trials classified as "unspecified," we manually reviewed additional trial documents and academic publications linked on ClinicalTrials.gov for any further information about pregnant inclusion. We also manually reviewed all "included" RCTs for accuracy.

For RCTs including pregnant participants, we further categorized conditions studied using GPT-4o into those focused on labor/delivery, pregnancy conditions (eg, preeclampsia), preterm labor prevention/treatment, pregnancy symptoms (eg, nausea), non-infectious chronic conditions (eg, asthma, Type I diabetes, depression/anxiety), infectious diseases, and other, manually reviewing all classifications. Last, as comparisons to other conditions affecting women and men of childbearing age but without fetal health implications, we separately cataloged RCTs related to infertility, erectile dysfunction, and abortion/treatment of fetal demise and manually reviewed these classifications.

We report the number and proportion of RCTs by group, using z-tests to compare by pregnancy enrollment. Analyses were conducted with R4.3.0 and GPT-4o. Further methodological details and code are available at: https://github.com/abilinski/GuiltyWithoutTrials.

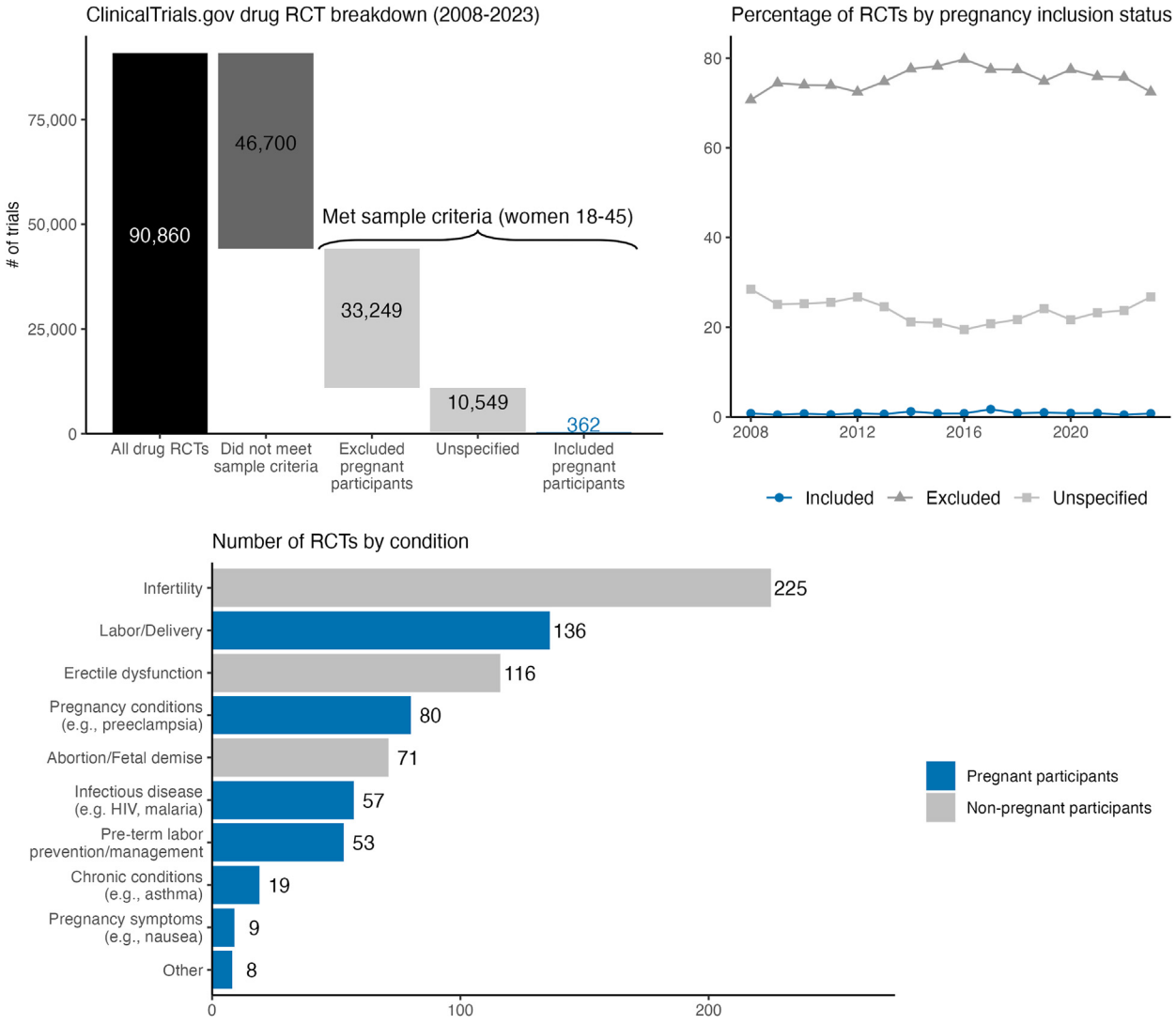
RESULTS: Of 90,860 RCTs posted from 2008 to 2023, 44,160 (49%) met sample criteria. Of these, 362 (0.8%) included pregnant participants, 33,249 (75%) excluded them, and 10,549 (24%) did not specify pregnant participation (Figure). These proportions were stable over the study period (eg, 0.8% in 2023). Nearly all RCTs including pregnant participants excluded non-pregnant participants (n=339, 94%). We found no evidence of pregnant inclusion our subsample of studies marked as "Unspecified" (n=50); in 41/50 (82%), we found evidence suggesting pregnant exclusion (Appendix).

Compared to RCTs excluding pregnant participants or not specifying pregnant participation, RCTs enrolling pregnant participants were more likely to be open label (40% vs 30%, $P<.001$) and focused on prevention (34% vs 5%, $P<.001$) (eg, interventions to forestall preterm labor, infections, and mother-to-child HIV transmission) rather than treatment (58% vs 80%, $P<.001$) (Supplemental Table). RCTs enrolling pregnant participants were less likely to be industry-funded (23% vs 77%, $P<.001$).

Of 362 RCTs including pregnant participants, 136 (38%) were focused on labor/delivery, 80 (22%) on pregnancy-related conditions, and 53 (15%) on preterm labor (Figure). Others studied infectious disease (n=57, 16%) (for example, malaria (n=19), HIV (n=15)), chronic conditions (n=19, 5%), and pregnancy symptoms (n=9, 2%). Outside of "included" RCTs, we identified 225 RCTs related to infertility, 116 to erectile dysfunction, and 71 to abortion/fetal demise treatment.

DISCUSSION: We comprehensively catalog pregnant inclusion in clinical trials from 2008 to 2023, extending prior work that has examined subsets of trials, typically over shorter time horizons.[6−9] Despite calls to include pregnant participants in RCTs,[1] enrollment has remained steady over 15 years. While pre-existing non-infectious conditions affect a growing share of pregnancies,[1] only 19 RCTs have addressed these, in marked contrast to many RCTs for other conditions such as

FIGURE
Pregnant Enrollment in Drug Randomized Clinical Trials (RCTs) on ClinicalTrials.gov



Top left. ClinicalTrials.gov drug RCT breakdown. "All drug RCTs" includes all registered randomized drug trials posted from 2008 to 2023. Sample criteria included gender (included female participants), age (included individuals 18—45), RCT status (not Withdrawn prior to enrollment or Unknown), and location/funding (US location, US government-funded, or industry-funded). Top right. RCTs over time by pregnant inclusion. Bottom. RCTs by condition (2008—2023).

RCT, randomized clinical trial.

infertility and erectile dysfunction. This work highlights the ongoing need for rigorous pregnancy-specific evidence. More pregnancy-specific RCTs are needed to improve data available to providers and ensure that pregnant individuals can receive high-quality, evidence-based care. ■

DATA AND CODE AVAILABILITY: Data and code are available at https://github.com/abilinski/GuiltyWithoutTrials.

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SUPPLEMENTAL TABLE

Randomized clinical trial (RCT) characteristics by pregnancy inclusion

Variable	Included pregnant participants (%)	Excluded pregnant participants or unspecified (%)	Excluded pregnant participants (%)	Unspecified pregnant inclusion (%)[a]
Total, n	362	43,798	33,249	10,549
Primary purpose				
Prevention	124 (34)	2189 (5)[b]	1692 (5)[b]	497 (5)[b]
Treatment	211 (58)	34,884 (80)[b]	26,090 (78)[b]	8794 (83)[b]
Basic science	6 (2)	2684 (6)[b]	2169 (7)[b]	515 (5)[c]
Funding				
Industry	83 (23)	33,705 (77)[b]	24,953 (75)[b]	8752 (83)[b]
NIH	51 (14)	3477 (8)[b]	3147 (9)[c]	330 (3)[b]
Location				
US	281 (78)	28,175 (64)[b]	21,308 (64)[b]	6867 (65)[b]
Masking				
Open label	146 (40)	13,179 (30)[b]	10,303 (31)[b]	2876 (27)[b]
Single	28 (8)	2667 (6)	2057 (6)	610 (6)
Double plus	188 (52)	27,905 (64)[b]	20,849 (63)[b]	7056 (67)[b]

Of 90,860 drug RCTs from 2003 to 2023 on ClinicalTrials.gov, these 44,160 RCTs met sample criteria and included women 18 to 45; 46,700 did not meet sample criteria. Numbers in parentheses show percentage of column total.

[a] We reviewed a random sample of studies marked unspecified (n=50) and found no evidence of pregnant inclusion. In 41 of 50 (82%) studies reviewed, there was evidence suggesting pregnant exclusion (Appendix): for 11 (22%), we found trial documentation specifying exclusion, 12 (24%) had no mention of pregnant participants in published academic papers, and 4 (8%) were phase I studies. Of the remaining, another 9 (18%) studied medications strongly contraindicated in pregnancy, and 5 (10%) studied medications with very limited pregnancy data; [b] $P<.001$, for z-test of proportions comparing included vs corresponding column; [c] $P<.01$, for z-test of proportions comparing included vs corresponding column.