# FDA Perspective: Regulatory Pathways for Inclusion of Pregnant and Lactating Persons in Clinical Trials

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# Disclaimer

- I do not have any financial disclosures to report
- This presentation represents the views of the speaker, and do not represent the official position of the FDA

Image credit PAHO at https://www.paho.org/en/news/22-9-2020-paho-reports-more-60000-confirmed-cases-covid-19-pregnant-women-458-deaths

# FDA Perspective

- FDA is committed to advancing research in pregnant and lactating people

- Active in national efforts: Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC); Duke Margolis-FDA workshop; OWH &JHU-CERSI Real World Data Maternal Health Conference

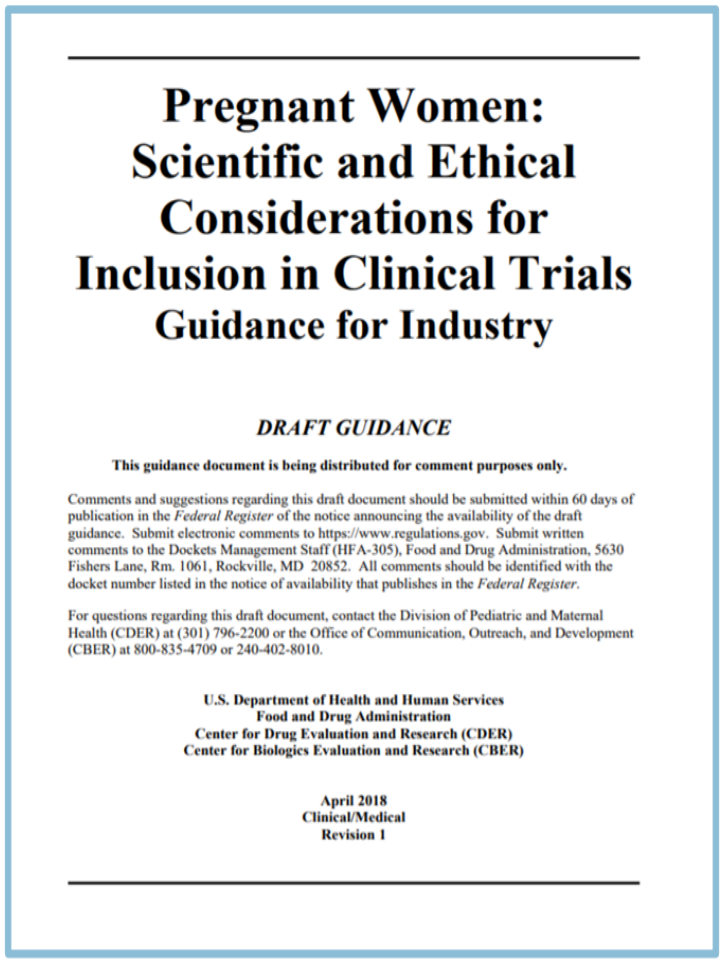
https://www.123rf.com/photo_40910245_pregnant-woman-symbol-stylized-vector-sketch.html

# Touchpoints

- Discuss the regulatory considerations for drug research and development for pregnant and lactating persons
  - Guidances
  - Implementation of subpart B and Common Rule changes
- Discuss selected FDA efforts to advance clinical trials and to collect data in pregnant and lactating people
  - Sentinel
  - CURE Pregnancy Treatment Repository

https://www.nationalreview.com/corner/apple-adds-pregnant-man-emoji-to-ios-keyboard/

# Guidances



**Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials**
**Guidance for Industry**

***DRAFT GUIDANCE***

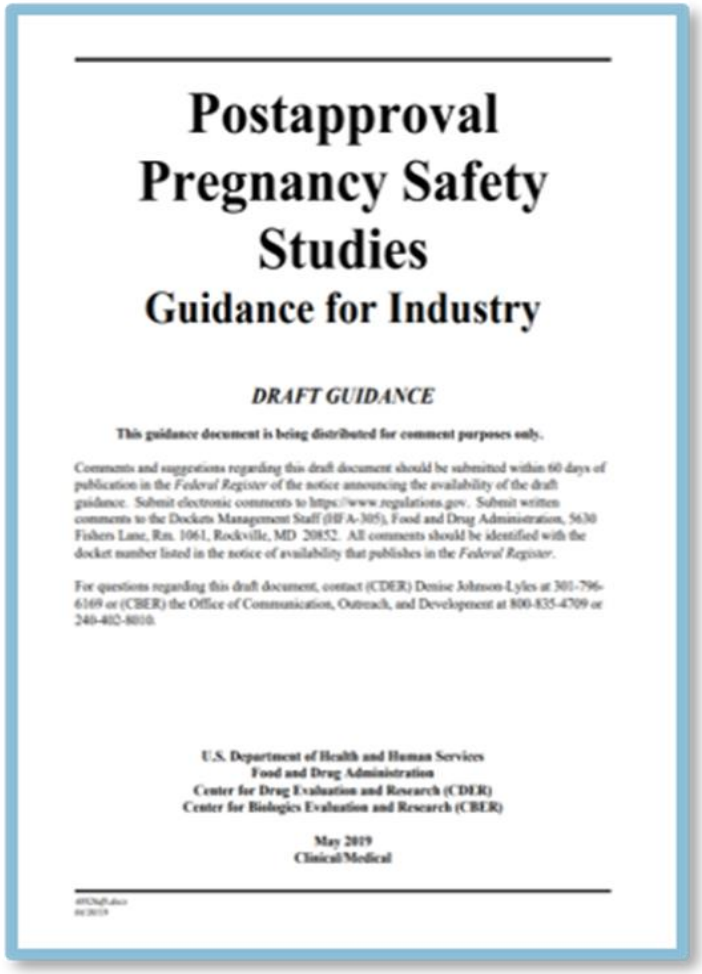
**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact the Division of Pediatric and Maternal Health (CDER) at (301) 796-2200 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**April 2018**
**Clinical/Medical**
**Revision 1**



**Postapproval Pregnancy Safety Studies**
**Guidance for Industry**

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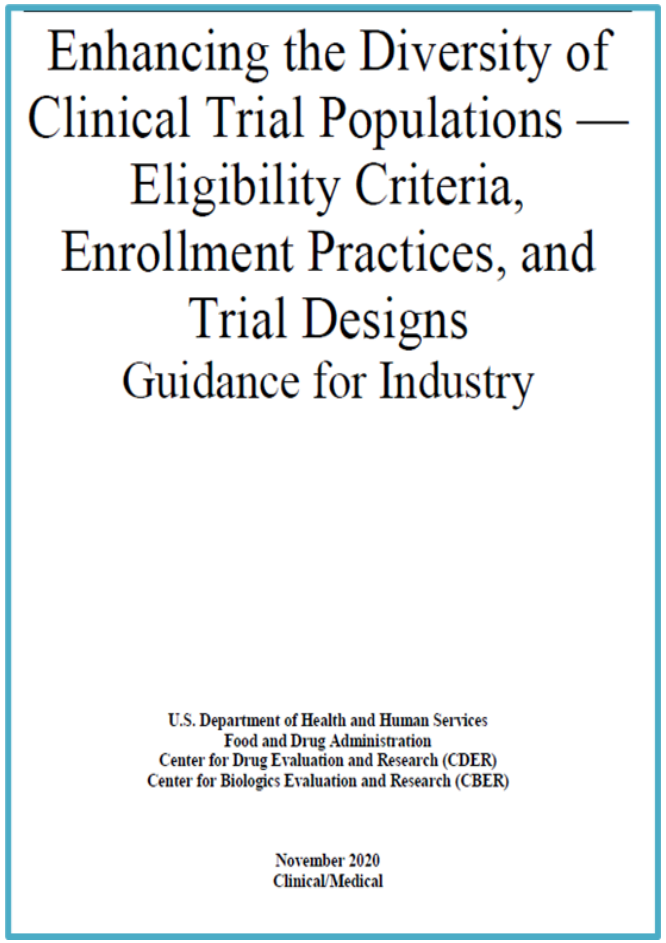
For questions regarding this draft document, contact (CDER) Denise Johnson-Lyles at 301-796-6169 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**May 2019**
**Clinical/Medical**

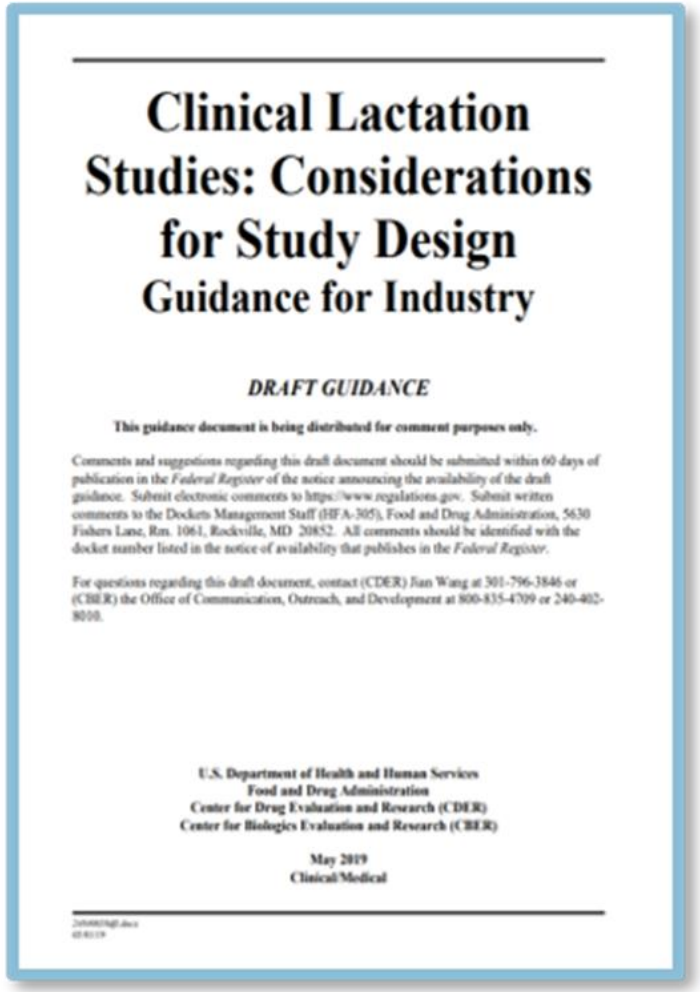


Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**November 2020**
**Clinical/Medical**

# Guidances



Clinical Lactation Studies: Considerations for Study Design

Guidance for Industry

*DRAFT GUIDANCE*

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For questions regarding this draft document, contact (CDER) Jian Wang at 301-796-3846 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Clinical/Medical

- Provides guidance on when lactation studies are warranted
  - Drugs expected to be used by lactating individuals
  - Study design and analysis considerations
- Opportunistic Study (vs. intervention study)
  - Lactating individuals prescribed the drug as part of clinical care
  - Data on amount of drug in breast milk
  - Infant safety data

# Federal Regulations 45 CFR part 46 ("Common Rule"), subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (1)

10 specific requirements intended to safeguard rights, welfare and safety because of additional/unknown risks:

- Prospect of direct benefit to the woman or fetus; if no benefit, the risk to the fetus must be minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

  Minimal Risk* (45 CFR 46.102 (i)): "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

- If the prospect of direct benefit is solely for the fetus, then additional consent from the father is needed, unless he is unavailable, incompetent, has temporary incapacity or the pregnancy results from rape or incest
- No inducements for pregnancy termination
- Investigators not involved in decisions re: pregnancy termination
- Investigators not involved in determining the viability of a neonate

*FDA regulations define minimal risk similarly (21 CFR 50.3(k))

Applies to research conducted or supported by HHS; FDA recommends

# Federal Regulations 45 CFR part 46, subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (2)

- Where scientifically appropriate, nonclinical studies (including in pregnant animals) and clinical studies have been conducted and provide risk information
- Least possible risk for achieving the objectives
- Informed consent is obtained as described in subpart A
- Participants are fully informed of the reasonably foreseeable impact of the research on the fetus or neonate
- For children who are pregnant, assent and permission are obtained

Note: All of these apply to research conducted or supported by HHS; FDA recommends

# Regulatory Progress

- 2018 Common Rule revised to remove reference to pregnant people as “vulnerable” to coercion or undue influence
  - Separate from and does not affect the applicability of Subpart B

- FDA working to harmonize its regulations with the Common Rule and remove the term “vulnerable” when referencing pregnant people in our human subject protection regulations (21 CFR part 56, IRBs)

Image credit:
http://enablemagazine.co.uk/long-read-disability-pregnancy-and-me/

# Data Sources: FDA's Proposed PDUFA VII Commitments, Sentinel: Pregnancy Safety

- Sentinel is the FDA's medical products active safety surveillance system
  - Mother-infant linkage: 79.1%
  - Descriptive analyses, inferential analyses, signal identification

- By Sep 30, 2023:
  - Public workshop on post-marketing safety studies in pregnant people

- By Sep 30, 2024:
  - Publish a workshop report describing the proposed framework

- By Sep 30, 2027:
  - Update the proposed framework, develop a guidance or MAPP/SOPP for a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs

i. Pregnancy Safety

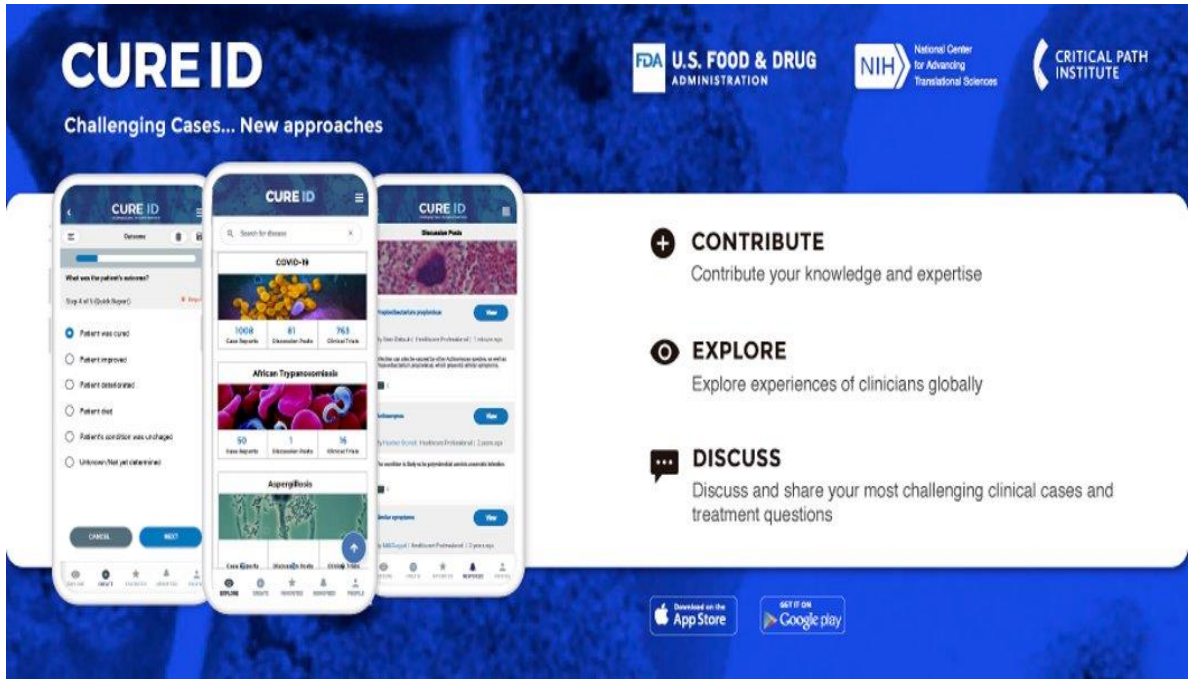
The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner.

(1) FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of post-market studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects. The framework would consider factors such as, but not limited to, purpose of study, types of post-market studies, anticipated exposure in females of reproductive potential (FRP) and pregnant women, potential toxicity of the drug and proposed risk mitigation, benefits of the drug, and magnitude and type of risk to be detected. The framework would specifically address the use of pregnancy registries and electronic healthcare data sources including Sentinel, with a goal of ensuring the most efficient means of obtaining highest quality safety data available.

https://www.fda.gov/media/151712/download

# Data Sources:
# CURE ID and Cure Pregnancy Treatment Repository

- Collect information on how existing drugs are being used clinically, so promising candidate(s) can be identified and clinical trials can be conducted to investigate potential new uses
- Cure Pregnancy Treatment Repository
  - Funded by a grant from OWH 2020-2022
  - Capture case reports in a treatment registry of pregnant patients treated with repurposed drugs for infectious disease
  - Include pregnancy-specific questions in the app; conduct outreach
  - Goal to identify drugs used to treat pregnancy-specific conditions as well as medical conditions that affect pregnancy



# Considerations to Further Address Barriers

- Inclusion should be the default; justify exclusion
- Engage in discussions early in drug development; provide guidance to researchers/IRBs
- Publicize priorities regarding therapeutic areas in pregnancy and lactation
- Targeted incentive program + require studies “PRGLAC Study Plan”

https://www.forbesindia.com/blog/work-place-human-resources/breaking-breastfeeding-barriers-for-working-women/

# Acknowledgements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