

Ethical Considerations in the Design and Conduct of Clinical Lactation Studies

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Balancing Benefits and Risks

- When a lactating woman takes a drug and the drug is present in human milk, the infant is exposed to both the benefits offered by the human milk and the risks from the drug, which the infant does not need for its own health.
- There are well-documented benefits of breast-feeding for the infant and the mother, and women will need to decide whether to breast-feed their infants while taking drugs.
- For most drugs, there is little or no scientific information about the amount of drug in human milk, the effects on milk production, or the effects of the drug on the breast-fed infant.
- When the amount of drug in human milk is unknown, the infant may be exposed to risks from the drug.



Clinical Investigation

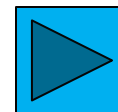
- A clinical investigation study involves a test article (i.e., drug or biological product), one or more human subjects, and either is subject to the investigational new drug application (IND) regulations or is being conducted to support a future research or marketing application (21 CFR 50.3(c)).
- A clinical investigation study following administration of a marketed drug or biologic in the course of medical practice may be IND exempt under 21 CFR part 312; however, the use of that drug or biologic meets the definition of a test article.
- A test article is any drug or biologic that is subject to FDA regulation regardless of its status as an investigational drug (21 CFR 50.3(j); 21 CFR 312.3(b); 21 CFR 56.102(l)).

Human Subjects

- As a recipient of the test article, the lactating woman who receives the drug or biologic during a clinical lactation study meets the definition of a human subject.

21 CFR 50.3(c) and 21 CFR 56.102(e)

- Thus, clinical lactation studies are subject to the human subject protections found in 21 CFR parts 50 and 56.
- *Her breast-feeding infant may also be a human subject if the infant may be exposed to test article via breast milk.*
- If so, the additional protections for children involved as subjects of research (21 CFR 50, Subpart D) may apply.





General Justification of Research Risk (Adult/Pediatric)

- Criterion for IRB approval of research.
 - Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.

21 CFR 56.111(a)(2); 45 CFR 46.111(a)(2)
- This criterion is modified by the additional protections for children enrolled in clinical investigations and/or research in that there is a limit to the risk that knowledge can justify.



Additional Safeguards for Children

21 CFR 50 Subpart D

- Research involving children either
 - must be restricted to “minimal” risk or a “minor increase over minimal” risk absent a potential for direct benefit to the enrolled child, or
 - must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.

21 CFR 50.51/53;45 CFR 46.404/406

21 CFR 50.52;45 CFR 46.405

Evaluating Research Risks

- When evaluating the research risks of the clinical lactation study, only those risks and benefits to the lactating woman and her breast-feeding infant that may result from research participation should be considered (21 CFR 56.111(a)(2)).
- The risks associated with drugs that the lactating woman receives as treatment for a medical condition in the clinical setting should not be considered a research risk when evaluating the risks of the clinical lactation study.
- This distinction affects both the ethical assessment of the infant's involvement and the informed consent/parental permission disclosures.

Sufficiently “Low” Risk?

- When lactating women are treated with a drug for a medical condition in the clinical setting, inclusion of infants in a clinical lactation study may be approvable by an IRB under either 21 CFR 50.51 or 50.53 (if the required conditions are met).
- Research must not involve “greater than minimal risk” (§50.51) unless the research would be likely to provide generalizable knowledge about the infant’s “disorder or condition” (§50.53).
- If the woman continues to breast-feed while enrolled in a clinical lactation study, the breast-fed infant has a condition of potential exposure to the drug. Hence, these infants could be exposed to a minor increase over minimal risk (§50.53) if the research is likely to yield generalizable knowledge of vital importance for understanding the effects of drug exposure on breast-fed infants.



Prospect of Direct Benefit?

- The administration of the drug to the lactating woman, and potential exposure of the infant to that drug, does not provide a prospect of direct benefit to the infant, because the drug is not being administered in response to the infants' own health needs.
- Other than a possible narrow exception when the risks of using alternative infant foods exceeds the risks of drug exposure through continued breast-feeding, the inclusion of infants in a clinical lactation study is not allowable under 21 CFR 50.52.

Defining the Study Population

- There are three populations of lactating women who could potentially participate in a clinical lactation study:
 - *Clinical Setting*: Lactating women who begin or are maintained on drug treatment for a medical condition in the clinical setting
 - *Research Setting*: Lactating women who begin an investigational drug for a medical condition in the research setting
 - *Volunteer Setting*: Healthy, lactating women who volunteer to receive the drug solely for research purposes
- These three potential study populations involve different ethical considerations, including whether the infant is a study subject and whether there are research-related risks to the breast-fed infant.

Three Areas of Concern

- 1) Separating the maternal decision to use a medically necessary drug from the decision to participate in a clinical lactation study.
- 2) Defining the risks to the breast-fed infant that occur as a result of the research.
- 3) Obtaining informed consent and parental permission.



Context: Clinical Setting

- Lactating women who begin or are maintained on drug treatment for a medical condition in the clinical setting, and who choose to continue breast-feeding during treatment, provide a unique opportunity to collect data on infants who may be exposed to the drug via breast milk.
- In addition to the collection and analysis of breast milk samples, a clinical lactation study should document potential drug exposure and assess safety in infants.
- It would be unethical to fail to assess the extent and effect of potential drug exposure on the infant via breast milk, or to ask a lactating woman to suspend breast-feeding for the purposes of participating in a clinical lactation study under these circumstances.
- When feasible, the individual results should be made available to inform the lactating woman, her clinician, and the infant's pediatrician about the extent of infant exposure to the drug.

Clinical Setting (1)



- 1) Separate the maternal decision to use a medically necessary drug from decision to participate in a clinical lactation study.
 - ✓ When considering infant feeding options, a lactating woman and her health care provider need to weigh the benefits of breast-feeding (and the potential risks of discontinuing breast-feeding) against the potential risks of exposure to the drug through human milk.
 - ✓ After a lactating woman and her health care provider decide to begin or continue a drug for treatment of her medical condition, it is reasonable to discuss participation in a clinical lactation study of that drug.
 - ✓ Clinical lactation studies that enroll women who need medication to treat a chronic or acute condition should be designed in a manner that: (1) separates the maternal decision to use a medically necessary drug from the decision to participate in a clinical lactation study; and (2) ensures that women are not unduly influenced to change their breast-feeding practices as a result of participation in a clinical lactation study.

Clinical Setting (2)

2) Defining the research risks to the breast-fed infant.

- ✓ The infant's mother already uses (or has decided to use) the drug as part of her own medical treatment before study enrollment.
- ✓ If mother also decides to continue breast-feeding, the infant is a human subject because the infant may be exposed to a drug via breast milk.
- ✓ However, infant's potential drug exposure through human milk is not considered a research risk, because the infant's exposure to the drug exists regardless of the woman's participation in the clinical lactation study.
- ✓ Thus, research risks to the infants in this setting are limited to any assessments that are performed to evaluate drug exposure to the infant. The risks of these assessments must present no more than minor increase over minimal risk to be approvable under 21 CFR 50.53.

Clinical Setting (3)

3. Obtaining informed consent (IC) and parental permission.
 - ✓ Drug administration is not a research intervention; thus, drug risks and potential benefits do not require discussion in IC process or document.
 - ✓ Research interventions (e.g., symptom diaries, human milk/plasma sampling) and any reasonably foreseeable risks or discomforts must be described in the IC process and document.
 - ✓ Purposes of clinical lactation study must be described, including fact that amount of infant drug exposure via breast milk is unknown.
 - ✓ If the lactating woman reconsiders her decision to continue breast-feeding before or during participation in the study, the investigator should refer the woman back to her health care provider and the infant's pediatrician to discuss options for infant feeding.
 - ✓ For infant involvement, investigators must obtain parental permission.

21 CFR 50.25(a)(1) and (2); 21 CFR 50.55

Research Setting (2)



- 2) Defining the research risks to the breast-fed infant.
- ✓ Infant drug exposure through human milk is a research risk and must be evaluated under 21 CFR part 50, subpart D.
 - ✓ Risk is greater than minimal risk (§50.51); infant does not have condition of ongoing drug exposure through continued breast-feeding independent of woman's decision to participate in research (§50.53); no prospect of direct benefit to infant from exposure to the investigational drug (§50.52).
 - ✓ Absent IRB referral and federal review under 21 CFR 50.54, breast-feeding must be discontinued until sufficient data about infant drug exposure are available to assess the risks and benefits of resuming breast-feeding.
 - ✓ Caveat: there may be a narrow exception where infant feeding with alternative formula carries greater risk and less benefit than continued breast-feeding during maternal exposure to the investigational drug

Research Setting (3)



3. Obtaining informed consent (IC) and parental permission.
 - ✓ Informed consent (IC) process and document must include a discussion of the potential drug-associated risks and benefits to the woman, the risks and benefits of other study interventions, and the risks and benefits of receiving treatment outside of the research.
 - ✓ In the limited settings where it is ethically appropriate for breast-feeding to continue during the study, the informed consent process must also address potential risks and benefits to the infant related to ongoing breast-feeding, potential exposure to the drug through human milk, and infant feeding with alternative infant foods.
 - ✓ Parental permission for the exposure of infants to the drug, and for drug-exposure and safety assessments on the infants, must also be obtained.

21 CFR 50.25(a)(1) and (2); 21 CFR 50.55

Context: Volunteer Setting

Two Possible Scenarios

- 1) Lactating women who are healthy volunteers and want to continue breast-feeding.
- 2) Lactating women who are healthy volunteers but who never start or choose to stop breast-feeding before study participation.

Volunteer Setting (1)

- 1) Lactating women who are healthy volunteers and want to continue breast-feeding.
 - ✓ Infant drug exposure through human milk is a research risk, as the woman chooses to expose herself and her breast-fed infant to a drug she would not otherwise use.
 - ✓ Exposure of the breast-fed infant to the drug means that infants are human subjects in the research, and thus a determination under 21 CFR part 50, subpart D, for their participation is necessary.
 - ✓ Administration of a drug to a healthy lactating woman who intends to continue breast-feeding would expose the infant to greater than minimal risk without a prospect of direct benefit, and is not approvable absent IRB referral and review under 21 CFR 50.54.

Volunteer Setting (1)

- 1) Lactating women who are healthy volunteers and want to continue breast-feeding.
 - In limited situations, a study may be permissible if:
 - ✓ Drug cleared within short period of time (e.g., 5 half-lives \leq 24 hours), limiting time period during which breast-feeding suspended.
 - ✓ Woman agrees not to feed her infant breast milk produced during period of drug exposure (e.g., until \geq 5 half-lives of drug have passed).
 - ✓ Drug not expected to interfere with resumption of breast-feeding.
 - A clinical lactation study that conforms to the above conditions would not expose an infant to the drug. Thus, the infant would not be a human subject, and the additional protections required under 21 CFR part 50, subpart D, would not apply.

Volunteer Setting (2)



- 2) Lactating women who are healthy volunteers but who never start or choose to stop breast-feeding before participation.
- Practical and scientific obstacles may prevent participation in a clinical lactation study for a lactating woman who recently delivered and either stopped or never began breast-feeding.
 - ✓ Mature milk samples are generally needed for such studies.
 - Some lactating women may decide to stop breast-feeding for personal or medical reasons and may want to participate in a clinical lactation study.
 - ✓ Accurate data on human milk drug concentrations may require maintaining milk production until study completion.
 - ✓ If the infant does not receive any human milk containing drug, the infant is not a human subject. However, the decision to stop breast-feeding should be independent of study participation, and no incentives should be offered that may influence this decision.

Three Settings - Summary



- 1) In the clinical setting, if a maternal decision to use a medically necessary drug is clearly separate from the decision to enroll in a clinical lactation study, the risks of drug exposure to the breast-feeding infant are not part of the research. As such, the study may be able to proceed under 21 CFR 50.53.
- 2) In the research setting, the risks of drug exposure to the breast-feeding infant are part of the research. Absent federal review and approval under 21 CFR 50.54, breast-feeding must be discontinued (absent a narrow exception). However, breast milk samples could be provided for drug testing.
- 3) In the healthy volunteer setting, the infant must not be exposed to breast milk that may contain the investigational drug. Breast feeding could be resumed after the study.

Concluding Comments

- A key consideration in evaluating the risk to which a breastfeeding infant may be exposed is whether the drug is being administered to a lactating woman to treat a maternal condition.
- After a drug has been started or continued for a maternal indication, there may be limited circumstances where a clinical lactation study may be acceptable following an independent decision by the lactating woman to continue breastfeeding.
- Absent a maternal condition that warrants treatment, a clinical lactation study involving a “healthy volunteer” would only be acceptable if the breastfeeding infant will not be exposed to the drug.

Thank you.

