

The Ethical Design and Conduct of Clinical Lactation Studies

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Clinical investigation...

- means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.
- For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.



Research Subjects

- In addition to the lactating woman, the breastfeeding infant (as a potential recipient of the investigational drug) is considered a subject of a clinical lactation study.
- As such, the additional protections for children involved as subjects of research (21 CFR 50, Subpart D) apply.



Key Distinction

- Is the drug being administered for a maternal condition that warrants treatment?
 - Investigational Product (Pre-Marketing)
 - Clinical/Research Use of a Marketed Product
- Is the lactating woman a “healthy volunteer”? (i.e., no maternal condition)



Subpart D Risk Categories

- For research not offering the prospect of direct benefit, the allowable risk exposure must be restricted to either minimal risk or a minor increase over minimal risk
21CFR 50.51 & 50.53
- For research that offers prospect of direct benefit, the allowable risk exposure can be more than a minor increase over minimal risk (i.e., greater than minimal risk)
21CFR 50.52



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Subpart D: Additional Protections for Children

	Direct Benefit	No Direct Benefit
Minimal Risk	21CFR50.51	21CFR50.51
Greater than Minimal Risk	21CFR50.52	21CFR50.53



Subpart D: Additional Protections for Children

	Direct Benefit	No Direct Benefit
Minimal Risk	Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in <u>daily life</u> or during the performance of <u>routine physical or psychological examinations or tests</u> .	
Greater than Minimal Risk		

21 CFR 56.102(i)



Subpart D: Additional Protections for Children

	Direct Benefit	No Direct Benefit
Minimal Risk	Minimal Risk	
Greater than Minimal Risk	21CFR50.52	21CFR50.53



Subpart D: Additional Protections for Children

Minimal Risk	Criteria for Approval: 1) Risk justified by anticipated benefit to subjects. 2) Relation of anticipated benefit to risk at least as favorable as available alternative approaches.	
	21 CFR 50.52	21 CFR 50.53



Subpart D: Additional Protections for Children

	Direct Benefit	No Direct Benefit
Minimal Risk	Minimal Risk	
Greater than Minimal Risk	Prospect of Direct Benefit	21 CFR 50.53



Subpart D: Additional Protections for Children

Criteria for approval:

- 1) only a minor (or slight) increase over minimal risk
- 2) experiences reasonably commensurate with actual or expected situation
- 3) yield generalizable knowledge of vital importance for understanding or amelioration of disorder or condition

Greater than
Minimal Risk

Prospect of
Direct Benefit

Minor Increase
over Minimal Risk



Subpart D: Additional Protections for Children

	Direct Benefit	No Direct Benefit
Minimal Risk	Minimal Risk	
Greater than Minimal Risk	Prospect of Direct Benefit	Minor Increase over Minimal Risk



Incremental Research Risk

- In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research).

21 CFR 56.111(a)(2)



Three Situations

- A. Lactating women continuing drug treatment for a maternal condition or beginning a new drug treatment for a maternal condition.
- B. Lactating mother is a healthy volunteer who continues breastfeeding her infant.
- C. Lactating mother is a healthy volunteer who stops breastfeeding or pumps and discards her milk during the period of drug exposure.



Lactating mother continuing/starting drug treatment for maternal condition

- Many women with chronic medical conditions continue required drug treatment throughout pregnancy.
 - Their fetuses are exposed to higher transplacental doses of maternal medication during gestation than they will experience as breastfeeding infants following delivery if their mothers choose to breastfeed.
 - In these situations, the benefits of breastfeeding may often outweigh the risks of continued lower dose exposure to a drug that the infant was already exposed to during gestation.



Lactating mother continuing/starting drug treatment for maternal condition

- Decision to begin drug treatment for maternal condition is a difficult one for any lactating woman who wants to continue BF her infant.
- Considerations
 - Risks and potential benefits to herself of the medication
 - Risks to her breastfeeding infant
 - possibility of drug exposure through breast milk
 - risks of discontinuing breastfeeding in light of known benefits to infant
- Clinical lactation studies provide better information on which to make these difficult judgments
 - There may be alternative treatments available with a lower documented transmission into breast milk or a better safety profile based on existing neonatal and/or pediatric studies (including juvenile animal models).



Lactating mother continuing/starting drug treatment for maternal condition

- After a lactating woman begins a clinically indicated medication for the treatment of a maternal condition, it is reasonable to approach her about the possibility of participating in a clinical lactation study of that medication.
- However, given the health benefit of breastfeeding for an infant, the decision to enroll in a clinical investigation should not interfere with a lactating woman's assessment of the risks and benefits of breastfeeding her infant.
- The maternal decision to start a clinically indicated medication should be kept separate from any subsequent decision to enroll in a clinical lactation study of that medication.



Lactating mother starting/continuing drug treatment for maternal condition

Implications for clinical lactation studies.

- Lactating woman who is breastfeeding should not be approached about participation in clinical investigation unless absolutely essential to her personal health and well-being, and no reasonable alternative treatments.
- Under these circumstances, prudent mother may decide to stop breastfeeding given absence of any information about effect of investigational product on infant.
- It may be appropriate to exclude lactating women who desire to continue breastfeeding from some clinical investigations (such as pre-market studies of NME) to protect infants from excessive and unknown risks.



Lactating mother starting/continuing drug treatment for maternal condition

Implications for clinical lactation studies.

- Investigator must obtain adequate informed consent for clinical lactation study of maternally-indicated drug, including risks of exposure of infant
- Lactating woman who continues to BF should have been informed by clinician about risks of drug to infant, but information given by investigator may be seen as new
- Process of informed consent for clinical lactation study may impact on woman's prior and independent decision to continue BF as she reflects on risks of drug to infant
- If so, investigator should refer woman back to clinician for further discussion of clinical risks and benefits of drug for herself, and risks and benefits of continued BF infant



Lactating mother starting/continuing drug treatment for maternal condition

Implications for clinical lactation studies.

- Risk of drug to exposed infant may not need to be considered research risk under Subpart D
- Research risks may not include drug exposure
 - infant exposed to drug even if not participating in study
 - include involvement of infant in assessing study objectives
 - E.g., weighing before/after BF, PK, PD and biomarker blood sampling, physiologic parameters, safety measures to evaluate possible AE of drug exposure
- Must present no more than minor increase over minimal risk to BF infant given absence of direct benefit (§50.53).
- Given clinical decision of lactating woman to take drug for maternal condition, infant can be considered to have condition (“at risk” due to drug exposure through BF)



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Lactating mother is a healthy volunteer who continues breastfeeding (BF) infant

- Exposure of BF infant to drug is "clinical investigation" and must be evaluated under 21 CFR 50, Subpart D.
- Absent direct benefit to BF infant, restrict to minimal risk (§50.51) or no more than minor increase over MR (§50.53)
- Exposure of BF infant to any drug administered for clinical lactation study presents more than minimal risk (MR).
- Even if drug has sufficient safety profile to be no more than minor increase over MR (unlikely), BF infant must have "disorder or condition"
- Infant of BF mother not disorder or condition under §50.53
- Thus, use of healthy lactating woman who intends to keep breastfeeding not approvable under 21 CFR 50, Subpart D



Definition of Condition

- a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future.

– IOM Recommendation 4.3



IOM Report on Research Involving Children 2004

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Lactating mother is healthy volunteer who stops BF
or pumps/discards milk during drug exposure

- If lactating woman asked to enroll at birth, there are scientific and practical obstacles to study participation as she needs to express milk for significant period of time before useful samples would be obtained.
- BF woman may decide independently to stop BF infant for personal or medical reasons
 - Held to ethical and regulatory standards for enrollment of healthy adult volunteer in clinical investigation under 21 CFR 50 and 56.
 - If infant does not receive breast milk containing study drug, Subpart D would not apply.



Lactating mother is healthy volunteer who stops BF
or pumps/discards milk during drug exposure

- Decision to stop BF breastfeeding should not be affected in any way by the possibility of enrolling in a clinical investigation.
 - Given the health benefits of breastfeeding, an infant whose mother discontinued breastfeeding for the purposes of enrolling in a clinical investigation would be placed at inappropriate and unjustified risk.
 - It may be difficult to ensure that a woman's decision to stop breastfeeding her infant is not influenced by her decision to enroll in a clinical investigation.
 - At the very least, a clinical lactation study should not provide any financial or other incentives to encourage participation of breastfeeding women who might otherwise continue breastfeeding their infants.



Lactating mother is healthy volunteer who stops BF or pumps/discards milk during drug exposure

- Alternatively, a lactating mother could decide to pump and discard her milk during the period of potential drug exposure for her infant.
 - Given the risk of intermittent bottle-feeding to successful breast-feeding, enrollment should be limited to breastfeeding women who have already demonstrated that short-term substitution of bottle-feeding using expressed breast milk would not undermine the resumption of breast-feeding.



Conclusions

- 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.

