

Developing Rational Guidance for Pregnancy Testing in Clinical Trials: Origin and Rationale

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My background

- Trained in obstetrics & gynecology
- Post-residency degree in epidemiology
- Research experience includes
 - Health services research using administrative data
 - PI of clinical trial of nicotine replacement during pregnancy
 - PI of data centers for multi-center clinical trials network in reproductive medicine and registry for devices used to treat uterine fibroids
 - Steering Committee for Phase III trials of HPV vaccine
- Major emphasis
 - Using simulation models to synthesize evidence for informing clinical and policy decision making
- Duke IRB for over 15 years



Pregnancy Testing at Duke

- Charles B. Hammond
 - Post-residency training in Ross lab at NIH 1966-1968, working on early assays for hCG
 - Established reference lab for hCG at Duke in early 1970's
 - Southeastern Regional Trophoblastic Disease Center
 - Became 3rd chair of department in 1980

Pregnancy Testing at Duke

- As institution, Duke was
 - Early adopter of quantitative serum hCG, but
 - Late adopter of urine testing for hCG
 - Both clinically and in research
- Even after adoption of urine testing for clinical indications, IRB policy still required serum testing
- “Need to use the most sensitive test possible”

Pregnancy Testing at Duke

- Evaluating screening policies major portion of my work
 - Emphasis on negative and positive predictive values rather than sensitivity/specificity
 - Prior probability of condition as important as test characteristics
- Began using this rationale to advocate for new IRB guidelines for deciding when urine testing would be acceptable for research

Prior Probability Makes a Difference

- Pregnancy rate approximately 10% in Phase III trials of HPV vaccine
 - Contraceptive use mandated, pregnancy testing prior to each dose
- Predictable based on study population
 - Women 18-24 → Very high ability to get pregnant
 - Sexually active → At risk for pregnancy
 - Effectiveness of contraceptive methods ≈ 90%

Pregnancy Testing at Duke

- Began using this rationale to advocate for new IRB guidelines for deciding when urine testing would be acceptable for research
- Frequently asked to help resolve conflicts between institutional policy and investigator/sponsor protocols
 - Impression that there was substantial inconsistency in pregnancy testing protocols in clinical research
 - Reinforced by consultation request regarding problem of false positive test results

Pregnancy Testing in Clinical Research

- Why can't we approach design of pregnancy testing in clinical research the way we approach cancer screening?
 - “Easy” part
 - Sensitivity and specificity of test
 - Prior probability of condition
 - Estimate positive and negative predictive value
 - Estimate likely outcomes of different strategies
 - Hard part
 - Consensus on optimal predictive values, trade-offs between benefits, harms, costs/burden
- Approached CTTI with idea, and here we are

Goals for the Meeting

- Review
 - Why we do pregnancy testing in clinical research
 - Methods for doing pregnancy testing in clinical research
 - Types of tests
 - When to test
 - How are decisions about methods being made now?
 - “Comparative effectiveness” of different methods
- Feedback and input
 - What important general principles should be considered in designing pregnancy testing protocols?
 - What information/guidance would be most useful to the research community, and ultimately, research subjects?
 - What resources would be most helpful for helping disseminate information/guidance?
 - Are there major evidence gaps that should be addressed through specific research?

Session I

Topics

- Rationale for Pregnancy Testing in Research
- Technical Aspects of Pregnancy Testing
- FDA and Pregnancy Testing

Questions to Consider

- Is an approach that tries to define the acceptable risk of a false negative test on a study-by-study basis reasonable?
- What criteria should a specific test meet in order to be considered for use in clinical research?
- How should those criteria be demonstrated, and who should document it?
- Is the use of home pregnancy testing ever acceptable, and if so, under what circumstances?

Session II

Topics

- Current practices
 - One sponsor's experience
 - Survey results

Questions to Consider

- Is the evidence that there is variability in current approaches to pregnancy testing strong enough to justify attempts to create greater consistency?
- Are there best practices that we can point to?
- What are the trade-offs between standardization and flexibility?

Session III

Topics

- Comparing estimated outcomes of different testing strategies

Questions to Consider

- Is this a useful approach?
- If so, are there ways to make the model more accurate and useful?
- If modeling results are useful, what is the best way to provide access to them (e.g., presentation of results for common scenarios vs. allowing users to run their own scenarios?)

Thank you!

