CTTI Pregnancy Testing in Clinical Trials: Summary of Day 1

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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?

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Overview

- Key Points from Presentations
- Key Points from Breakout Sessions

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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?

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I: Why We Test

- Females of reproductive potential participate in all phases of clinical research
- High background risk of fetal loss, congenital anomalies
- Teratogenicity can happen any time during pregnancy
- Even with preclinical testing, most late phase trials start with high degree of uncertainty about specific risk of teratogenicity
- Focus on clinical trials is on
  - Preventing exposure
    - Contraception
    - Pregnancy testing before enrollment and study intervention
  - Minimizing duration of exposure
    - Intermittent pregnancy testing after enrollment

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II: Measuring hCG

- Multiple variants of hCG→potential impact on sensitivity and specificity of testing
- Lack of standardization in assays→variation in measured concentrations, detection of clinically relevant hCG variants
  - Variability in quantitative measurements
  - "Variant hook"→false negatives in later pregnancy
    - Consistency choice of test during study
- Analytical sensitivity varies with brand (home and POC)
- Cutoffs often not in agreement with manufacturer's claims/package insert
  - Usually lower levels than reported

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II: Measuring hCG

- Timing of testing relative to start of pregnancy affects how early hCG can detect pregnancy
  - Patient estimate of when menses will occur may be inaccurate to normal variation in cycle length
- False positive hCGs can occur
  - Interfering antibodies
  - Pituitary hCG (ovulation or perimenopause)
    - FSH can help discriminate
  - Exogenous hCG

III: FDA Regulation of Pregnancy Tests

- Class II device
  - Approved under 510(k)
  - "Substantial equivalence" to predicate device
- Cutoff for claims
  - Concentration that yields 50% positives and 50% negatives
- Newer tests include examination for variant hook effect from β-core fragment
- Typically 100 subjects used to establish clinical "substantial equivalence"
- Few reports of inaccurate results in postmarketing surveillance

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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?

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IV: Industry Perspective

- No plan for minimizing pregnancy exposure is perfect
  - Estimates from Phase III studies <0.1 percent/cycle
- Pregnancy tests intended for use in diagnosis (suspected pregnancy), not screening
  - Expect different positive and negative PVs
  - Need for confirmatory testing increases burden on subjects, investigators, and sponsors

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IV: Industry Perspective

- At one sponsor, all interventional clinical studies enrolling females of childbearing potential require pregnancy testing
  - Prior to enrollment unless intent to enroll pregnant subjects
  - Post-enrollment periodic testing, with some exceptions
    - Intervention withheld for positive or indeterminate results
    - More rigorous protocol for known teratogenic risk
  - Most at end of treatment or early withdrawal

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IV: Industry Perspective

- Outcomes of pregnancy testing depend on a complex process that involves more than just sensitivity/specificity and timing of test
  - Communication of results, actions taken based on results also key
- Guidance for pregnancy testing should be
  - Evidence-based (as much as possible)
  - Separate standards, recommendations, best practices and provide rationale
  - Need to consider operational feasibility at all levels

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V: Survey Results

- 50% of respondents→maximum acceptable risk of pregnancy < 1/10,000
  - Choices for testing options inconsistent with that standard
- NPV consistently rated most important consideration, followed by patient burden
- Variation in type of testing by risk to fetus, but home testing OK for 5-10% of respondents
- Most recommended
  - Continued post-enrollment testing unless very short duration study
  - After study, depending on PK
- Free text responses→some consider age, contraceptive method

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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?)

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VI: Model Parameters

- Subject Age
- Hysterectomy Status
- Menopausal Status
- Menstrual Cycle Characteristics
- Age-specific Contraceptive Method use
- Pregnancy Outcome Probabilities
- Contraceptive Effectiveness (Typical Use)
- hCG Levels in Non-pregnant women
- hCG Levels in Pregnancy
- Sensitivity of hCG assays
- Probability of detecting symptoms in the absence of testing

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VI: Model results

- Fewer pregnancies with age
  - Fewer women of childbearing potential due to menopause, hysterectomy
  - Greater use of highly effective methods (particularly sterilization)
  - Lower probability of getting pregnant
- Fewer detected pregnancies when testing not performed relative to menstrual cycle
  - 9-10 day window when ANY pregnancy test will be negative

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VI: Model Results

- False positive results
  - Increase with age
  - Only when threshold for positive test 5-19 IU/L
- Estimated absolute differences in false negative rates relatively small
  - Young women→difference between 5 and 20 IU/L about 5/1000, decreasing to 3/10,000 in perimenopausal women

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Summary of Breakout Sessions

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Are there other factors that should be considered in the modeling approach and for resource development?

- Typical vs perfect contraception use
  - *Model currently uses "typical" use;*
- Duration of pre-enrollment use less than 12 months
  - *Can be readily modified, but remember that estimates based on Pearl index will underestimate failure rate early, overestimate later*
- Duration of counseling
  - *Could incorporate, but need evidence that to associated with effectiveness*
- Co-morbidities
  - Motivation to avoid pregnancy
    - *Could accommodate in a variety of ways`*
  - Inherent decreased fertility
    - *Could include, but need estimates for how much a given condition affects fertility*

Are there other factors that should be considered in the modeling approach and for resource development?

- Potential litigation risk (even in a simplified way)
  - *Can estimate overall likelihood of miscarriage and length of duration of exposure now*
  - *Would need way to estimate likelihood of*
    - *Miscarriage or congenital anomaly conditional to exposure*
    - *Likelihood of litigation given miscarriage/anomaly*
- Consider the phase of the study (in determining level of risk)
  - Wouldn't need to be incorporated in the model—model outputs risk of pregnancy based on population and testing protocol→sponsor/regulator decides whether that's acceptable
- Factor in 9 day window/timing of testing
  - *Already in model, can explore alternative strategies to incorporate impact of 9 day window (e.g., home LH kits)*

Are there other factors that should be considered in the modeling approach and for resource development?

- Cost: Is opaque. Recognize that cost is a factor that needs to be considered. Not binary choice, but do what's best for trial – leave to judgment of trial designer.
  - *Could include cost as a user-modifiable variable*
- More analytic information in model (more granularity).
  - *If on-line "TurboTax" format, can allow as much granularity as desired*
- Feasibility (cognitive dissonance). Risk is very low, but drives us toward infeasibility. Separate risks of test with risk of human pregnancy – find most accurate pregnancy test, use serum test when you need to.
  - M*ight be benefit of including cost →forces decision maker to see consequences of trying to achieve very low risk of pregnancy*
- Data on initial test, but not follow-up testing throughout the trial. Can follow-up testing be modeled? Data available? Risk to pregnancy if identified late -- what is acceptable risk? Can there be a risk threshold? Specify risk and then model? Benchmarking? Reflect what risks are.
  - *Follow-up testing in model, can be extremely flexible with both timing and choice of test*

What resources do you currently use to develop pregnancy testing protocols for clinical trials?

- Standard of care for specified patient population
- Investigator/opinion leader recommendations
- Literature review
- ICH guidelines
- Institutional (sponsor, hospital) standards
  - *How to resolve if in conflict?*
- Institutional experience
  - *Cognitive bias*

What additional resources are needed to help support the development of pregnancy testing protocols for clinical trials?

- Major evidence gaps
  - Risk of pregnancy in pre-approval studies
  - Risk factors for pregnancy in pre-approval studies
    - Leverage existing resources to get data
- General information on
  - Biology of reproduction and early pregnancy (background risk of miscarriage and congenital anomalies)
  - Biology of hCG (9 day window, levels during pregnancy, false positives, variants)
  - Performance characteristics of available hCG tests
  - Contraceptive effectiveness
    - *?Different levels for patients, study staff, investigators, sponsors*
- Broad guidelines/recommendations/best practices based on above considerations
- Resources to ensure ongoing update of evidence, evaluation of model/recommendations

What are the patients' perspectives on the proposed resources?

- Better information on (including degree of certainty)
  - Risks to fetus/embryo from
    - Exposure to study intervention
    - Maternal condition
  - Risks to mother from
    - Exposure to study intervention (i.e., risks changed because of physiologic changes in pregnancy)
    - Maternal condition (e.g., PAH, depression)
  - Risk of becoming pregnant during trial based on age and contraceptive method
  - Risks of pregnancy testing
    - False negatives and false positives
    - Additional burden above other required study activities
- Engage patients/potential subjects as partners early in the protocol development stage
  - *PCORI?*

How do you envision using these resources in designing pregnancy testing protocols for clinical trials?

- Define acceptable level of risk
  - ***These resources will NOT do that—they will give estimates of WHAT the level of risk is. Whether that risk is acceptable is a judgment, not a calculation***
- Provide rationale for making decisions about testing
- Provide estimates of risk to allow testing to vary based on patient-specific risk
  - Across protocols
  - ?Within protocols

- Users
  - Background evidence (reproductive biology, testing performance, etc)
    - Patients, study teams, sponsors, regulators (tiered)
  - Interactive model
    - Study designers, regulators

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What would be the most useful format for the potential resources (e.g., broad guidelines or recommendations, tables, webpage or smart phone application to enter trial specific data)?

- Broad guidelines in multiple formats (publication, guidebook, online)
- Background information in multiple formats (publication, guidebook, online)
- Interactive estimates
  - "TurboTax"—online
  - Smartphone app—could potentially do things like estimate risk of pregnancy given age, contraceptive method