Regulatory Challenges of Clinical Trials in our Hospitals

Susan Kornetsky, MPH,
Senior Director, Clinical Research Compliance
Children’s Hospital, Boston
Our Current Environment

- Importance of pediatric trials continues to be a priority
- Pediatric Clinical trials often require multiple centers
- Single IRBs do not eliminate institutional practices and interpretations that are part of a human research protection program and pertinent to pediatrics
Some Challenges

- Risk/Benefit / Assessments
- Parental Permission/Assent
- Remuneration/Payments
- Turning Age of Majority
- Adolescent Issues
Risk/Benefit Pediatric Research

• “Sliding scale" for research involving children
  – classified into one of four categories according to the risk and the direct benefit to the child
  – as risk-benefit relationship of the research become less favorable, additional requirements must be satisfied, more protections

• Usually not problematic
  – Minimal risk research with or without potential benefit
  – Greater than minimal with potential for direct benefit

• Research or components of research presenting greater than minimal risk with no benefit
  – Additional ethical/regulatory criteria to approve

• Different IRBs may not make consistent determinations-
  Single IRB review may help this issue
Examples When No Potential for Direct Benefit

• Some phase I trials - single dose, short course
• Invasive Placebos (shams and infusions)
• Biopsies for research purposes only (muscle, endoscopies)
• Need for sedation for research tests and assessments (MRI)
Example 1

- DMD trial
- Double-blind, placebo-controlled, multicenter
- Administer once weekly intravenous infusions for up to 96 weeks
- Placement of central line/port raises risk/benefit issues for placebo group so need to do single IV peripheral vein infusions
- Requires 2 muscle biopsies - prior to study and after therapy - No benefit - Requires anesthesia
- Roll over to open label after 96 weeks
Example 2

- Drugs that involve intrathecal injection
- Perform sham instead of placebo injection
- Requirement to sedate older children otherwise may realize difference in injection versus sham
Other Examples

- MRI studies not required or useful for clinical care of children who may require sedation
- Phase 1 study of an investigational drug where only one or a few doses administered. Hard to claim any benefit yet if drug has not been tested may also be hard to consider minimal risk
Parental Permission/Assent

- Determine whether permission from one, two or no parents/guardians is required
- Determine whether assent of child/adolescent is required
- If assent required IRB decides how (Regulations do not dictate how)
- Wards/ Foster care present issues of who is legal guardian
Challenges for Multicenter Trials

• IRBs/Institutions have different standards
  – Age of assent
  – Form of assent - separate form, same form as parent, verbal
  – Who is permitted to obtain parental permission - PI or research coordinators
  – Use of waiver of parental permission

• State Laws
  – Mature and emancipated minors
  – Wards and foster care
Challenges

- Concept and content of assent differs age 8 or 16
- If subject is unable to assent when initially enrolled, is there a moral obligation to obtain assent when they become capable?
Remuneration / Payments

• Forms
  – Reimbursement for expenses
  – Compensation for time
  – Tokens of appreciation
  – Incentives

• What does parent versus child receive

• Could be age dependent

• Avoid use of child for benefit or parent

• Can this differ by site for multicenter trials? If so on what basis?
Turning Age of Majority

• When research requires continued intervention and interaction with “now adult”
  – Parental permission no longer valid
  – Consent of “now adult” needs to be obtained
  – Requires careful tracking of birthdays

• If research requires reviewing records/specimens created after a child turns 18
  – Require consent/authorization from “now adult”
  – Obtain waiver of permission from IRB
Example: Ongoing Intervention Trial

- Intervention trial
  - Subjects enter study at 13-15 years old
  - Followed for 5 years with intervention and assessments
  - Some subjects will turn 18
  - Need to obtain consent in order to continue to follow subject, continue assessments, record data for period after subject is 18
Biological Samples

• “If the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of “human subjects research” (for example, it involves the continued analysis of specimens or data for which the subject’s identity is readily identifiable to the investigator(s) then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver obtaining informed consent in order for the subjects to continue their participation in the research.”

• Differences between samples collected and coded versus biobank with links to identifiers
Example Repository/Registry Trial

- Samples/data collected with parental permission and assent from subjects 5-15 years of age
- PI continues to use samples/data when subjects turn 18
- If interaction/or continue to pull data/ left over clinical specimens, consent must be obtained
- If there is no interaction with subject when they turn 18
  - Is the subject’s identity readily identifiable to the PI?
  - If so, meets the definition of human subject and consent regulations apply
  - If not identifiable. IRB may waive consent
Potential Solutions/Considerations

• IRB grants waiver when situation arises (when subject actually turns 18)
• IRB grants waiver when protocol initially approved in anticipation of subjects turning 18
  – i.e. When IRB reviews protocol they recognize subjects will turn 18 in the future and in anticipation IRB includes approval of waiver for when subjects turn 18
Locating and Approaching “Now Adults”

- Long term follow-up common in pediatric research
- Often need to go through parent to find now “adult subject”
- Many at college or not at home
- Many requests to use social medial facebook and presents some regulatory and ethical challenges
- Do “now adults” even realize they were enrolled in research?
- Decisional impairment creates additional issues. In some cases continued legal guardianship needs to be established
Adolescent Issues

• Special issues regarding privacy and confidentiality

• Eligibility testing
  – pregnancy testing
  – screening illicit drug

• Sensitive information
  – drug and alcohol use
  – gender and sexual identity

• Consent issues
  – Parents not present during visits
  – Autonomy of adolescent
  – Differences of opinion
  – Waivers of parental permission
Conclusion

• Some of the issue raised are general challenges in pediatric research; however variability in multicenter trials increases complexity

• Single IRB review will not solve all the issues since some local policies will still exist

• Continued need for consensus and guidance on some of these issues

• Consider issues as pediatric protocols are developed. Build regulatory and ethical considerations in design and implementation