

To biopsy or not to biopsy – that is the question.

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Disclaimer

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
- Robert Nelson has no financial conflicts of interest to disclose.

Topics

1. The development of the ethical safeguards for children enrolled in clinical investigations.
2. The clinical and research paradigms – the challenge of obtaining sufficient tissue-based information to justify biopsy-driven treatment protocols.

Developing the Additional Safeguards for Children in Research

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (referred to as The National Commission) issued their Report and Recommendations on Research Involving Children in 1978.
- The ethical framework proposed by The National Commission was adopted as “subpart D” by HHS in 1983 (45 CFR 46) and FDA in 2001 (21 CFR 50).
- A review of their deliberations provides important insights into understanding the ethical framework.

Early Agreement

- Two types of pediatric research were agreed upon early in The National Commission's deliberations.
 - Research not involving greater than minimal risk (21 CFR 50.51).
 - Research where an intervention (note: “component analysis”) presents greater than minimal risk, but where the risk is justified by the anticipated direct benefit to the enrolled children and the relation of the anticipated benefit to such risk is at least as favorable as that presented by available alternative approaches (21 CFR 50.52).
- Reasoning by analogy, the National Commission argued that parents should be allowed to permit the inclusion of children in research that “mimics” activities in which parents are allowed to permit the participation of children (e.g., in the first case, activities of daily life and routine well child care; in the second case, necessary clinical care).

An “Escape Hatch”

- Limiting research interventions to these two categories may exclude important research presenting more than minimal risk without any direct clinical benefit to enrolled children.
- Discussion focused on defining criteria for use of the “escape hatch” and to clarify the process.
- Key Components
 - “Public review and comment” allowing oversight by “society.”
 - “Sound ethical principles” (i.e., apply ethical principles to “new and unanticipated state of affairs”)
 - “Serious health problem” of “major significance”
- Recommendation for a “National Advisory Board” (NAB) became 21 CFR 50.54/45 CFR 46.407 (federal panel review).

Not otherwise approvable (21 CFR 50.54/45 CFR 46.407)

- IRB determines that clinical investigation presents reasonable opportunity to understand, prevent, or alleviate serious problem affecting the health or welfare of children; and
- Secretary HHS/FDA Commissioner, after consulting expert panel and following public review and comment, determines:
 - The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - The clinical investigation will be conducted in accordance with sound ethical principles; and
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

FDA Meeting April, 2009

Topic: DIPG biopsy for “research only” purposes

Questions:

1. Has the state of the science in drug targeting research progressed to where there is a reasonable expectation of success in identifying drug candidates to move into early phase clinical trials for DIPG?
✓ Vote: 17 in favor, 6 opposed, 1 abstained
2. Should children with DIPG undergo a non-therapeutic brain biopsy to advance the study of possible drug targets (i.e. research purposes only)?
✓ Vote: 14 in favor, 10 opposed

Limiting Federal Referrals

- The National Commission developed a fourth category out of concern that frequent referral to a National Advisory Board would prove burdensome.
- To prevent this category from being abused if the research is viewed to be important, The National Commission added the restriction that the risks of interventions not offering a prospect of direct benefit must be no more than “a minor increase over minimal risk.”
- Even so, this category was (and continues to be) controversial, and provoked two dissenting statements in the final report.
- This recommendation for local IRB review of interventions that do not offer a prospect of direct benefit yet present only a minor increase over minimal risk became 21 CFR 50.53/45 CFR 46.406.

21 CFR 50 Subpart D

Additional Safeguards for Children

- Research involving children must either
 - be restricted to “minimal” risk or a “minor increase over minimal” risk *absent a potential for direct benefit* to the enrolled child, *or*
 - 21 CFR 50.51/53; 45 CFR 46.404/406
 - present risks that are justified by anticipated direct benefits to child; with the balance at least as favorable as any available alternatives, *or*
 - 21 CFR 50.52; 45 CFR 46.405
 - be referred for federal panel review if the research is not otherwise approvable yet presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
 - 21 CFR 50.54; 45 CFR 46.407
- ✓ In addition, all categories of research must meet the requirements for parental permission and child assent.
 - 21 CFR 50.54; 45 CFR 46.407

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2. The clinical and research paradigms – the challenge of obtaining sufficient tissue-based information to justify biopsy-driven treatment protocols.

Clinical Paradigm

- What would you do with the information?
 - Are the risks of obtaining the biopsy worth the potential benefit *to the patient* of the information to be obtained?
- Potential benefit of the biopsy?
 - The biopsy may be necessary to establish the diagnosis. Non-invasive testing may not be sufficient to adequately distinguish between diagnostic possibilities (e.g., emerging data suggest this may be the case with DIPG).
 - In general, this benefit to the patient can be either...
 - Therapeutic: allow for better treatment decisions by clinician
 - Prognostic: allow for better life decisions by patient/family
- Assumption: ≥ 2 diagnostic possibilities absent biopsy
 - Clarification: same phenotype, different drug targets = 2 diagnoses

Research Paradigm(s)

- 1) “Research Only” – no “actionable” intelligence.
 - The patient/family would need to be told that the information obtained from the biopsy would offer *no benefit* to the patient.
 - Are the risks of obtaining the biopsy worth the potential benefit *to future patients* of the information to be obtained?
- 2) Alternative: The biopsy information may serve as an important “branch point” in a clinical (treatment) protocol
 - Although there may be uncertainty about the relative merits of different treatment strategies, there is sufficient information about diagnostic subtypes to allow for biopsy-driven protocol decisions
 - In this case, the risks of the biopsy are balanced against the potential clinical benefit of the different treatment strategies (as is the case in the clinical paradigm)

The Challenge

- How do we obtain sufficient tissue-based information to justify biopsy-driven treatment protocols?
- Options:
 - Post-Mortem Tissue Specimens
 - Specimen biomarkers may be altered by treatments?
 - Only useful for limited set of biomarkers/drug targets (e.g., DNA)?
 - May introduce sufficient diagnostic uncertainty to justify performing pre-mortem biopsies to guide clinical decision-making
 - Animal Models
 - Appropriateness of animal model may require some knowledge of the human tissue biology which can only be obtained by biopsy
 - “Research Only” Biopsies
 - Requires asking patient and/or family to permit an invasive procedure that offers no clinical benefit to the patient

Additional thoughts on obtaining a (greater than minimal risk) biopsy

- The science of drug targeting in a specific disease needs to have matured to where there is a “reasonable assurance” that a “research only” biopsy may result in important knowledge.
- Other sources of tissue ought to be fully explored before putting patients at risk for the benefit of scientific knowledge.
- Approaching patients and/or families about obtaining such a biopsy must be performed by someone who is not involved in the clinical care of the patient.
- Clinical investigators who also care for these patients should be transparent about their conflicting commitments when recommending a biopsy be performed for clinical reasons.

Thank you.



Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting

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Outline

- Regulation of investigational medical products
- Tissue sampling for investigational use and for clinical care
- Variable risks for tissue sampling procedures
- Importance of tissue sampling for development of precision medicine
- Opinion varies as to the expectation and value of requiring Investigational Device Exemption (IDE) submission on the basis of risks arising from biopsy procedures

Regulation of Investigational Products

- Drugs
 - Investigational New Drug (IND) – Purpose of an IND is so that the product “may be shipped lawfully for the purpose of conducting clinical investigations of that drug.”
- Devices
 - Investigational Device Exemption (IDE) – The purpose of the IDE regulation is to encourage, to extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use...

CDRH purview includes the regulation of investigational in vitro diagnostic devices

- A Risk Determination from CDRH evaluates the level of risk of the use of a specific device in a specific trial
- Potential benefit does **not** influence this determination
- For Significant Risk determinations, an IDE is required

Investigational Device Exemptions

- ▶ IDE applications require:
 - ▶ The device must be clearly defined
 - ▶ The device must undergo a basic level of analytical validation
 - ▶ Informed consent form includes certain information

Purpose of IDE Review for Significant Risk Devices

- Determination that the risks to subjects do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained
- Complete specification of the device, for purposes of the investigation
 - May be essential for interpretation of results from a therapeutic product's biomarker-driven clinical trial; i.e. if you don't have an analytically validated device to measure the biomarker, trial results will be difficult to interpret
- Adequate informed consent for use of the device

Risks with Investigational use of In Vitro Diagnostic (IVD) Devices

- Patients may forego known effective treatment
- Patients may be exposed to excess adverse events with investigational treatment or additional diagnostic procedures
- Inaccurate detection/measurement of a biomarker that has known importance
- Harms from procedures used to obtain specimens for investigational use

Procedure-Related Harms in Medical Device Investigations

- Therapeutic devices (often implanted)
 - Medical procedure risks are associated with use of the device
 - Procedures often standardized, as part of the investigational protocol
- In vitro diagnostic devices
 - Medical procedure risks are associated with obtaining specimens for IVD testing
 - Specimen acquisition and IVD testing separated by space and time

Some purposes of tissue sampling in clinical trials

- Real-time use for investigational purposes within the trial (i.e. trial arm assignment)
- Archiving for later use investigating a specific diagnostic device
- Exploratory “basic physiological research” or “correlative science” that might drive development of a treatment and/or a diagnostic device
- Real-time use for diagnostic and/or therapeutic purposes according to standard of care

Risks with obtaining tissue depend on the sampling site, patient selection, and how the tissue is obtained

- Noninvasive or minimally invasive methods (blood draw, sputum, etc.)
- Lower risk biopsies
 - Skin, needle biopsy of peripheral or noncritical site
- Higher risk biopsies
 - Mediastinum, pancreas, brain

Risk of a specific biopsy procedure depends on

- Site of procedure
- Type of procedure
- Patient's disease and underlying health
- Institutional experience and support capabilities

- In the context of the trial, biopsy risk is assessed for each patient in real time and may to an extent be controlled according to the clinical judgment of the health care providers

Therapeutic Products and In Vitro Diagnostic Devices for Precision Medicine

- Recent and accelerating progress in oncology
- Treatment is often targeted, and selection often relies on IVD test result
- Expectation that IVDs will inform best use of anti-tumor agents
- Targeted treatment often involves tumors that are uncommon, based on, for example, age, histology, a biomarker

- FDA seeks advice about how sponsors and the Agency can best evaluate and control tissue sampling-associated risks in clinical investigations of in vitro diagnostic devices.

The bottom line

- With respect to the performance of a biopsy in the context of a clinical trial,
- FDA recognizes that biopsies are performed for purposes other than routine clinical care or device development
- If the biopsy is being used to develop an investigational in vitro diagnostic device, an IDE for the device may be needed