IDE Requirements for Diagnostic Tests Used in Clinical Trials

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Outline

• Background
• Uses of Markers
• Significant Risk
• IDE and FDA Pre-Submission Review
• The Need to Partner with Assay Developers
• Recommendation and Summary
These and other articles in lay and scientific press highlighted the risk for patients that are posed by new and poorly validated diagnostics.

Trialists & Investigators want to use markers but often do not understand the rigors of clinical assay development and validation.

The FDA Office of In Vitro Devices began to enforce its oversight authority over the safety of diagnostics used for medical decision making in clinical trials.

IOM 2010: “A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program”

Recommendation 7:
“NCI, in cooperation with other agencies, should establish a consistent, dynamic process to oversee the development of national unified standards as needed for oncology research”
Uses of Markers

**Integral Markers** –
- Markers that are essential for performance of the trial
  - used for medical-decision-making in specimen donor
  - results given back to patient or physician
  - types: eligibility criterion, treatment assignment, risk stratification, dose modification
  - must be performed in a CLIA-approved laboratory

**Integrated Markers** –
- Markers that are research markers
  - performed on all subjects but not for medical decision-making for them
  - performed on a predefined subset (e.g., QoL studies)
  - performed to test a hypothesis

**Research (Correlative) Markers** –
- Markers studied to generate hypotheses - exploratory
Examples of Integral Markers

• A Companion Diagnostic
  - especially if an eligibility criterion for receiving drug
    - EML4-ALK fusion in NSCLC – Crizotinib
    - mutation in EGFR in NSCLC - Erlotinib

• A risk stratification factor
  - FLT3-ITD, NPM1, CEPBα in AML
    - Marrow transplant with 30% Mortality

• Dose modification
  - Busulfan Pharmacokinetic Assay (COG AML)
The Investigational Device Exemption (IDE) regulations (21 CFR Part 812) require that Significant Risk (SR) device studies follow all of the IDE regulations and have an IDE application approved by FDA.

In general, a SR device is defined [21 CFR 812.3(m)] as an investigational device that:

• Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

• Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
Regulations - Significant Risk (SR)

- SR is independent of whether the device is to be marketed as a 510K or PMA or is used only as an integral marker in clinical trials.

- However, SR is not well defined or quantitated:
  Does not include IVDs

- Draft Guidance to IRBs about IND/IDEs addresses what/who to examine but not how to examine risk:
  “Guidance for IRBs, Clinical Investigators and Sponsors IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed” November 2012 – FDA document ucm328855

- Draft Guidance on Companion Diagnostics contains in footnote 5 that a “device with the therapeutic product allows the therapeutic product’s benefits to exceed its risks”
  July 2011 -FDA document ucm262292
  Perhaps this principle and how to measure it should be expanded in a separate guidance dedicated to risk!
What is An IDE?

- IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.
- Investigational use includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.
- All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.
  - An IRB may approve NSR IDEs but all IDEs that may have a Significant Risk need to be reviewed by the FDA
  - If any question about risk, the PI and assay developer should do a pre-IDE review with the FDA

PI Should Explain Potential of Marker For Risk in Protocol

• What is the risk to the patient of a false positive (FP) or negative (FN) assay result?

• This requires understanding the analytical performance of assays:
  • accuracy, reproducibility, precision and
  • how these characteristics translate into false positive or negatives
  • Analytical data will be different depending on the type of device/technology (DNA, gene expression, IHC, etc)

• Ideally, this should be provided by a collaborator from the clinical lab

• Is the risk of the device (marker) less than the benefit of the treatment?
A Non-Significant Risk Investigational Device Exemption (NSR IDE)?

- Clinical evaluation of devices that have been deemed Non-Significant Risk by IRB or FDA requires:
  - an IDE approved by an institutional review board (IRB).
  - informed consent from all patients
  - labeling for investigational use only
  - monitoring of the study
  - required records and reports.

Medical Devices: The Pre-Submission Program and Meetings with FDA Staff

- FDA has recently released a draft guidance on pre-submission for devices (assays)
- Outlines their current recommendations about clinical assay development
- Also suggests how to contact the FDA’s Offices

## Pre-IDE (Sub) Review vs Application

<table>
<thead>
<tr>
<th>Review time:</th>
<th>Pre-IDE review</th>
<th>IDE application</th>
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<td>30 Days</td>
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<table>
<thead>
<tr>
<th>Risk assessment:</th>
<th>Assay performance (rate of FP/FN within samples of intended use) impact of FP/FN on patient within state of disease in trial</th>
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</table>

<table>
<thead>
<tr>
<th>Elements of trial document reviewed for risk:</th>
<th>Background/significance/rationale, primary and secondary endpoints, eligibility criteria, statistical design, correlative science section, informed consent</th>
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</table>

<table>
<thead>
<tr>
<th>Assay assessment:</th>
<th>Analytical performance of assay within intended clinical use accuracy, precision, reliability, reproducibility</th>
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<tr>
<th>Elements of trial document reviewed for assay:</th>
<th>Not currently included in LOIs, concepts or protocols but information required is generally that needed for any test in a CLIA-accredited laboratory*</th>
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**Need to know what patients are told**

Clinical Assay Development Resources
From NCI

Clinical Assay Development Program:  http://cadp.cancer.gov/

Cancer Diagnosis Program:  http://cdp.cancer.gov

Cancer Diagnosis Program Templates for IHC, FISH/CISH, or Somatic Mutations:  http://cdp.cancer.gov/diagnostics/templates.htm

- also available on the CTEP website under templates and documents for protocols
- provide documentation of clinical assay performance for trials
An Integral Marker That is NOT a SR

• To date integral markers that are used for stratification during randomization in CTEP trials are considered to be NSR
  • Patient has same chance for risk of treatment

• However, integral markers that are used for eligibility criteria, treatment assignment, or dose modification of the patient in whom marker assayed may pose significant risk and may need a pre-sub (IDE) review

Patient has equal probability of receiving treatment A/B
What Does the FDA Look For In a Pre-Sub (IDE)

The reviews that we have seen from CDRH generally focus on the same issues:

- Accuracy
- Reproducibility (Precision)
- Interfering Substances
- Stability of the analyte(s)
- Linearity
- Limits of detection/quantitation
- Reference Interval
- Measurement Bias
FDA Follows The Clinical Laboratory Standards Institute (CLSI) Recommendations as CMS Uses for CLIA Laboratories

<table>
<thead>
<tr>
<th>Item</th>
<th>CLSI Document</th>
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<tbody>
<tr>
<td>Preliminary Evaluation</td>
<td>EP10-A3</td>
</tr>
<tr>
<td>Reproducibility (Precision)</td>
<td>EP15-A2, EP5-A2</td>
</tr>
<tr>
<td>Interfering Substances</td>
<td>EP7-A</td>
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<tr>
<td>Stability of the analyte(s)</td>
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<tr>
<td>Linearity</td>
<td>EP6-A</td>
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<td>Limits of detection/quantitation</td>
<td>EP17-A</td>
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<tr>
<td>Reference Interval</td>
<td>C28-A3</td>
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These documents are well known to your clinical laboratory colleagues
Recommendations For Protocols with Integral Markers

Investigators would be wise to include a section in a protocol that documents:

a) what is the risk of a FP or FN assay result
b) how the benefits of treatment are greater than risks caused by an assay FP or FN within context of disease
c) whether they think an IND or IDE is required

AND

Also in informed consent:
For protocols that include integral markers the consequences of FP and FN assay results should be described for patients in the consent.

Also helpful to include clinical assay developers as partners and collaborators on trials and members of the IRBs.
SUMMARY

- Protocol investigators, assay developers and performers, and sponsors need to collaborate/partner closely.
- If trial has an integral marker, then an IDE may be needed and IRB, investigator and sponsor need a pre-IDE submission to FDA.
- Can be hard for IRB and FDA to find the risk attendant to an integral marker.
  - Need to know how to define FP and FN rates and what that means for toxicity to patient.
  - Both IRB and FDA need to know what patient is told about the risk for patient in the consent.

Whether this increased attention to development of Molecular Diagnostics improves quality of care will need to be assessed.
Additional Back-Up

FDA has many guidance documents freely available on its medical device guidance page:

<table>
<thead>
<tr>
<th>Document</th>
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<tbody>
<tr>
<td>ucm33716</td>
<td>Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling</td>
</tr>
<tr>
<td>ucm085371</td>
<td>General Principles of Software Validation; Final Guidance for Industry and FDA Staff</td>
</tr>
<tr>
<td>ucm073779</td>
<td>Off-The-Shelf Software Use in Medical Devices</td>
</tr>
<tr>
<td>ucm262292</td>
<td>In Vitro Companion Diagnostic Devices</td>
</tr>
<tr>
<td>ucm094002</td>
<td>Guidance for Submission of Immunohistochemistry Applications to the FDA</td>
</tr>
<tr>
<td>ucm267831</td>
<td>Design Considerations for Pivotal Clinical Investigations for Medical Devices</td>
</tr>
<tr>
<td>ucm296379</td>
<td>Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications</td>
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Can be found at: [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)

NOT EXHAUSTIVE