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IDE Requirements for Diagnostic Tests Used in Clinical Trials

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Cancer Institute

Outline

- Background
- Uses of Markers
- Significant Risk
- IDE and FDA Pre-Submission Review
- The Need to Partner with Assay Developers
- Recommendation and Summary

BACKGROUND

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"

- **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.**

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

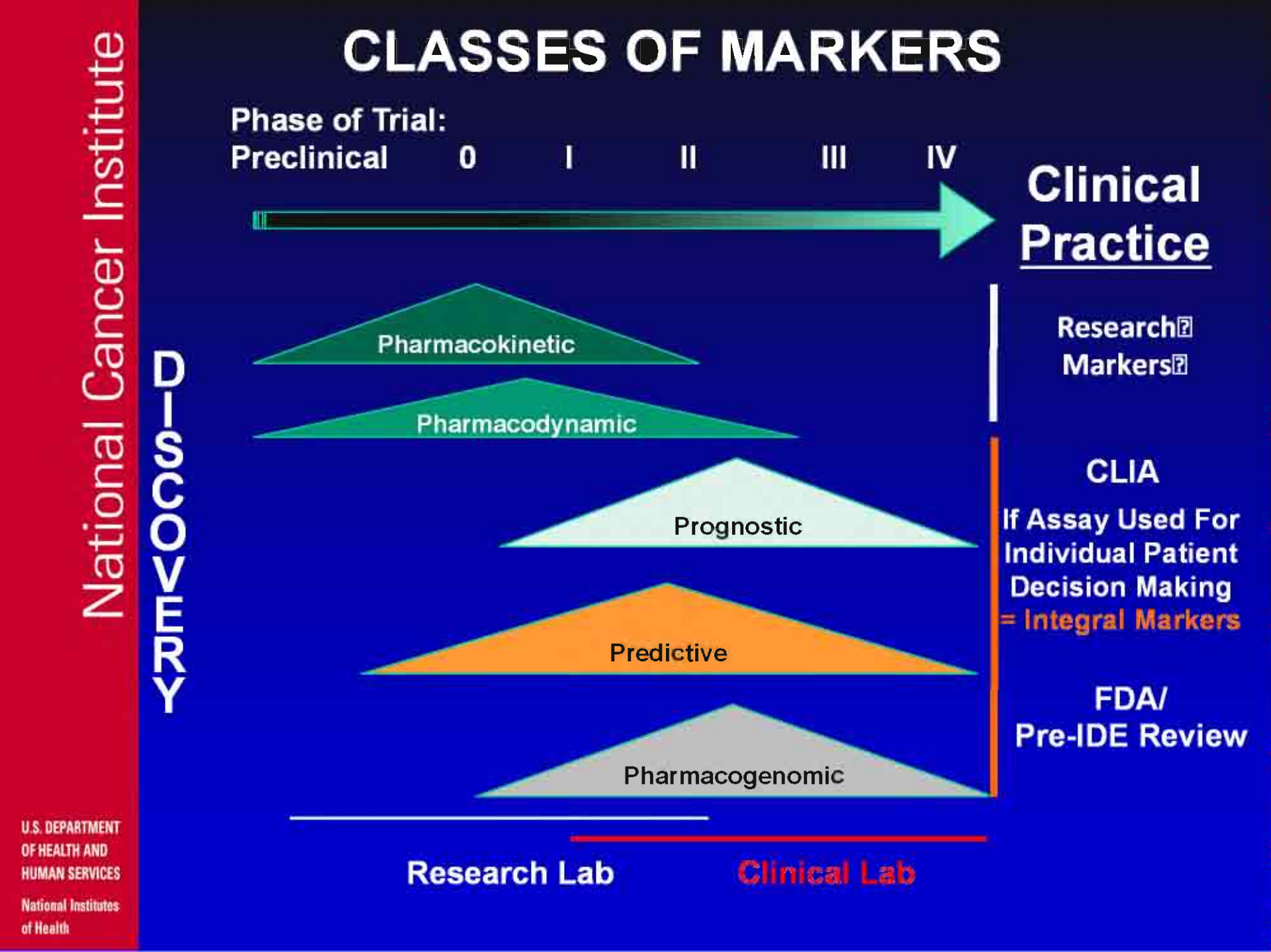
OR - performed on a predefined subset (e.g., QoL studies)

OR - performed to test a hypothesis

Research (Correlative) Markers –

- Markers studied to generate hypotheses - exploratory

CLASSES OF MARKERS



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)

Regulations - Significant Risk

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 to used only as an integral marker in clinical trials

- However, SR is not well defined or quantitated:

Guidance on SR: "Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies."
January 2006 – FDA document ucm126418

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

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm

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.

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm

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

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

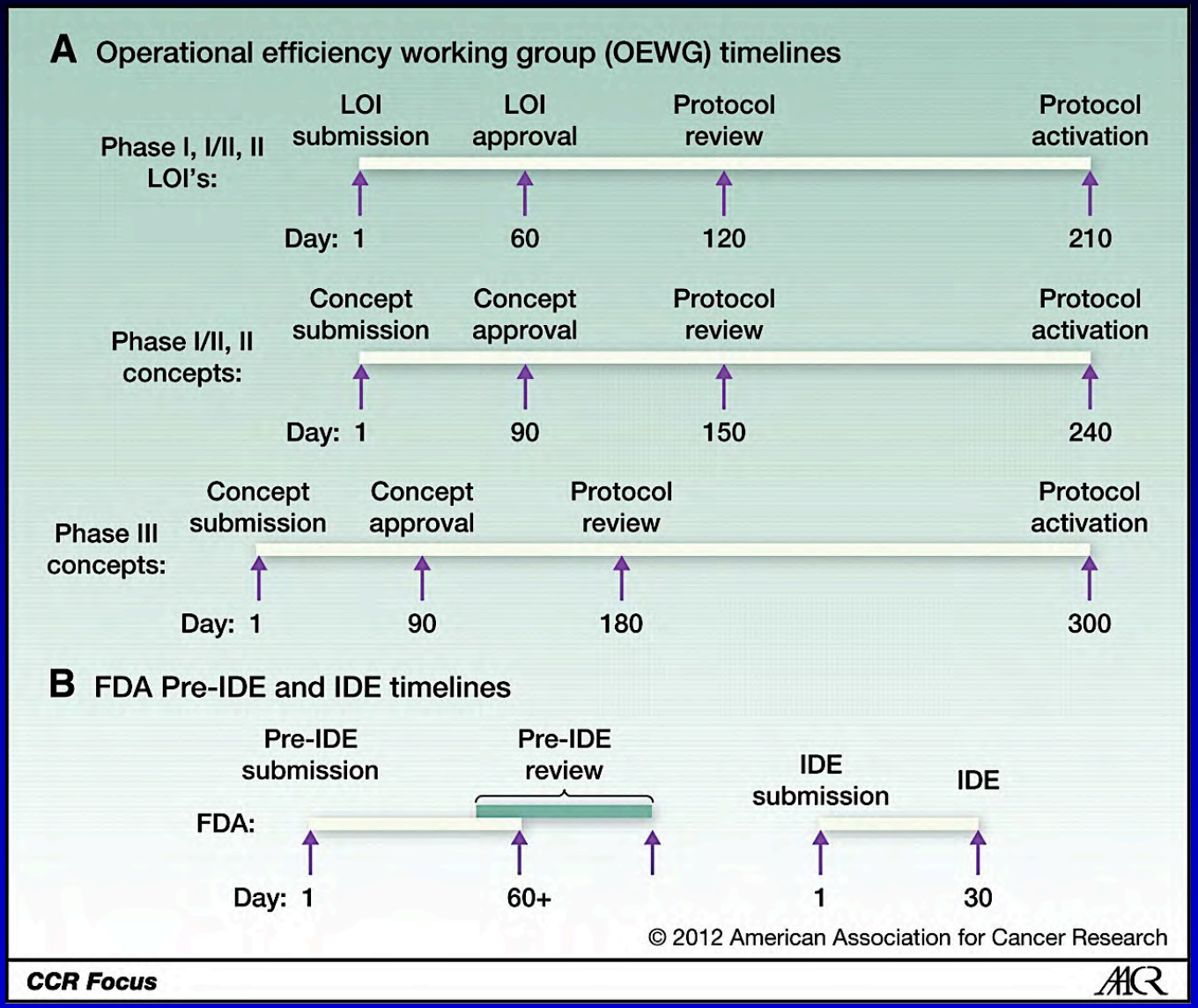
Pre-IDE (Sub) Review vs Application

	Pre-IDE review	IDE application
Review time:	~60 Days	30 Days
Risk assessment:	Assay performance (rate of FP/FN within samples of intended use) impact of FP/FN on patient within state of disease in trial	
Elements of trial document reviewed for risk:	Background/significance/rationale, primary and secondary endpoints, eligibility criteria, statistical design, correlative science section, informed consent	
Assay assessment:	Analytical performance of assay within intended clinical use accuracy, precision, reliability, reproducibility	
Elements of trial document reviewed for assay:	Not currently included in LOIs, concepts or protocols but information required is generally that needed for any test in a CLIA-accredited laboratory*	

Need to know what patients are told

Meshinchi et al. Clin Cancer Res 18:1547–54, 2012

Pre-IDE Review Meets OEWG



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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

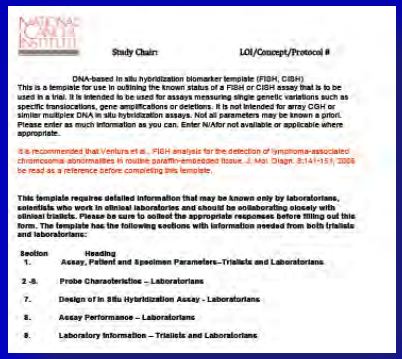

LOI/Concept/Protocol #: Protocol Investigator:

Immunohistochemical (IHC) Marker Template
For Integral Markers in Clinical Trials

This is a template to describe the analytical and clinical performance of an assay that is essential for performance of a trial. It will be used to assess whether assays are ready for use in a trial by Disease Steering Committees and CTEP. The FDA may also use it to evaluate integral assays and diagnostics for their pre-IDE evaluation. Not all parameters may be known a priori. Please enter as much information as you can and N/A for not available or applicable where appropriate.

This template requires detailed information that may be known only by laboratorians, scientists who work in clinical laboratories, and should be collaborating closely with clinical trialists. Please be sure to collect the appropriate responses before filling out this form. The template has the following sections with information needed from trialists and laboratorians:

1. Assay, Patient and Specimen Information –Trialists and Laboratorians
2. Primary Antibody Characteristics – Laboratorians
3. Design of Immunohistochemical Assay - Laboratorians
4. Assay Performance – Laboratorians
5. Laboratory Information – Trialists and Laboratorians


Study Chair: LOI/Concept/Protocol #

DNA-based in situ hybridization biomarker template (FISH, CISH)

This is a template for use in outlining the known status of a FISH or CISH assay that is to be used in a trial. It is intended to be used for assays measuring single genetic variations such as specific translocations, gene amplifications or deletions. It is not intended for array CGH or similar multiplex DNA in situ hybridization assays. Not all parameters may be known a priori. Please enter as much information as you can. Enter N/A for not available or applicable where appropriate.

It is recommended that Ventura et al., FISH analysis for the detection of lymphoma-associated chromosome abnormalities in routine paraffin-embedded tissue. J. Mol. Diagn. 8:141-151, 2006 be read as a reference before completing this template.

This template requires detailed information that may be known only by laboratorians, scientists who work in clinical laboratories and should be collaborating closely with clinical trialists. Please be sure to collect the appropriate responses before filling out this form. The template has the following sections with information needed from both trialists and laboratorians:

Section	Heading
1.	Assay, Patient and Specimen Parameters–Trialists and Laboratorians
2 -6.	Probe Characteristics – Laboratorians
7.	Design of In Situ Hybridization Assay - Laboratorians
8.	Assay Performance – Laboratorians
9.	Laboratory Information – Trialists and Laboratorians


Study Chair: LOI/Concept/Protocol #

DNA-based Mutation Assays

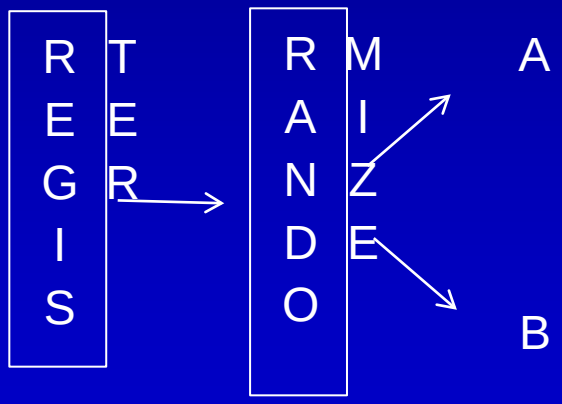
This is a template for use in outlining the known status of an assay that is to be used in a trial. The Clinical Laboratory Scientists who will be performing the tests should fill out this form. Not all parameters will be known a priori. Please enter as much information as you can. Enter N/A for not available or applicable where appropriate. This template is intended only for DNA-based somatic mutations and not for RNA-based mutations. It is also primarily intended for assays for markers that are integral for a trial. The information provided will be useful for an FDA pre-IDE review.

It is recommended that Jennings et. al. Recommended Principles and Practices for Validating Clinical Molecular Pathology Tests. Arch Pathol Lab Med 133:743-755, 2009 be read as a reference before completing this template.

Section	Heading
1	Assay, Patient and Specimen Parameters
2	Design of Mutation Assay
3	Assay Performance
4	Laboratory that is performing this assay

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



Stratify
Marker
Stage, etc.

Non-Significant Risk

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

Item	CLSI Document
Preliminary Evaluation	EP10-A3
Accuracy	EP15-A2, EP9-A2-IR
Reproducibility (Precision)	EP15-A2, EP5-A2
Interfering Substances	EP7-A
Stability of the analyte(s)	EP25-A
Linearity	EP6-A
Limits of detection/quantitation	EP17-A
Reference Interval	C28-A3
Measurement Bias	C51A, EP15-A2, EP9-A2

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

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Additional Back-Up

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

Document	Title
ucm33716	**Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommend-ations for Labeling**
ucm085371	**General Principles of Software Validation; Final Guidance for Industry and FDA Staff**
ucm073779	**Off-The-Shelf Software Use in Medical Devices**
ucm262292	**In Vitro Companion Diagnostic Devices**
ucm094002	**Guidance for Submission of Immunohistochemistry Applications to the FDA**
ucm267831	**Design Considerations for Pivotal Clinical Investigations for Medical Devices**
ucm296379	**Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications**

Can be found at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

NOT EXHAUSTIVE