

**Implementing
Imaging Standardization
in Multi-center Clinical Trials
for Investigational Drugs & Biologics**

George Mills, M.D., M.B.A.

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Implementing Standardization of Imaging Techniques

FDA's Critical Path Initiative

1. Imaging is a key technology for assessing, accelerating the development of, and guiding the use of new therapeutic options
2. The Agency believe that synergy between current drug development programs and current imaging techniques can be created for drug development to work in a more cost effective manner

Independent Review Charters (IRC)

IRCs Reviewed

2000 = 2

2003 = < 12

2006 (to date) = > 36

Imaging in Multi-center Clinical Trials

Requires

Multi-center Imaging Standardization

Current status - available multiple clinical centers

For all imaging modalities, Sponsor/CROs must assume **the participating clinical sites are not standardized with any other participating centers** for the following:

- imaging technique
- imaging platforms
- imaging archive

Individual sites = unique, individualized imaging

Imaging techniques = “Practice of medicine”

Sponsors/CROs

Implement multi-center imaging standardization

- A. Clinical trials protocol
- B. Investigators' brochure
- C. Onsite imaging manual

Specify “in detail” the specific imaging procedures & provide “at the minimum”

1. full description of the required imaging parameters
2. the imaging output: hard copy, digital
3. the imaging intervals – timeline schema
4. the necessary archive: hard copy & digital

Sponsor/CROs standardization

Clinical Sites prepared at the clinical site

1. Oriented to imaging for the clinical trial
2. Confirmed - functional to initiate the trial
3. Retested & monitored during the clinical trial

Essential elements for standardization

- Define & document the responsible imaging sub-investigators
- Onsite training the imaging sub-investigators
 - A. Radiologists
 - B. Technologists
- Phase 2 clinical trial experiences to establish & confirm standardized imaging acquisition and archive techniques across multi-centers

Essential elements for standardization

Establish the level of cross site-consistency & the known variances across clinical sites

- Within & across participating imaging systems
- Within & across all archive system

- Independent reader training
- Independent review
- Independent review charter

Essential elements for standardization

“HOW-TO” Clinical Sites Imaging Manuals Written for Radiologists & X-Ray Technologists

Images & Text

Description, examples & requirements

1. Imaging procedure with special positioning
2. Equipment with setup
3. Radiographic output – **DIGITAL** and/or film
4. Imaging archive

Essential elements to standardize

Prepare/Train/Monitor the clinical sites to avoid “drift”

- ✓ Imaging procedures – Onsite manual
- ✓ Phantom studies?
- ✓ Acquisition of required clinical history
- ✓ Case Report Form completion
- ✓ Imaging archive retention & performance

Imaging archive

- A. Archive of imaging at the clinical sites
 - B. Transfer of imaging for the Independent Review
 - C. Archive of imaging at the independent review site
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- ✓ Track & record all steps
 - ✓ Document all deviations

Independent Review Charter

Essential to define, link and relate

- ✓ the clinical protocol
- ✓ the statistical analytical plan

Prospectively designed, reviewed and approved by
the Agency prior to the initiation of Phase 3

Agency's critical review element to validate imaging results
At least as valuable as the images

“Precision is the goal of multi-center imaging”

- Implement the same, detailed imaging acquisition protocols at all clinical sites
- Clinical Trials Imaging = “Established” NOT “Cutting-Edge”
- Optimize image processing & reconstruction software
 - Avoid manual techniques as possible
 - Select & develop semi-automated -> automated
 - Reduce human interactions
- Avoid - “practice of medicine” imaging

Communicate early & often!

Direct line: 301-796-1419

New email address:

George.Mills@FDA.HHS.GOV

Thank you!

Multi-center clinical trials are able to establish

- ✓ Efficacy
- ✓ Safety

Imaging is able to establish in multi-center trials

- a) Targeting
- b) Therapeutic effects
- c) Safety Profile

Clinical results can be demonstrated in multi-center trials through independent review of imaging

1. Reproducibility
2. Precision
3. Safety

Imaging can establish

“Value added” information for

Drugs and/or biologics development

- Clinical safety
and/or
- Clinical efficacy

- WHO tumor response criteria
- RECIST tumor response criteria

Sponsors/CROs can not assume

Phase 2 trial – precursor trial for Phase 3

- Participating clinical sites
- Indicated population
- Imaging protocols
- Review & adjust imaging