Imaging Trials: ECOG-ACRIN

Paul Kinahan
University of Washington, Seattle, WA
Co-Chair, ECOG-ACRIN Imaging Core Laboratory

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Clinical Trial Imaging
Endpoint Process Standards
Guidance for Industry

DRAFT GUIDANCE
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
March 2015
Clinical/Medical
Revision 1
FDA Draft Guidance (paraphrased)

- Images serve diagnostic purposes even though local methods may [sic] vary
- Variability in image acquisition & analysis may have no medical significance
- In a clinical trial, imaging variability may limit ability to meet trial objectives
- We recommend that some trials augment these existing standards to create trial-specific imaging process standards

Imaging data from NCI-sponsored clinical trials

- National Clinical Trials Network (NCTN)
- NCI Community Oncology Research Program (NCORP)
Imaging Science Advisory Committee (ISAC)

1. Determining if the proposed use of medical imaging in a clinical trial advances the mission of ECOG-ACRIN
   - Should have the potential to reshape the future of patient care through clinical research, earlier disease detection, increased success of therapeutic interventions, greater rates of prevention, and better outcomes for patients

2. Ensuring appropriate use of medical imaging from ethical and technical/procedural standpoints

3. Reviewing imaging budgets
   - reasonable estimates for imaging costs and related components
   - source of funding is identified

4. Ensuring necessary prior reviews have occurred and that the PI had sufficient time to respond and satisfactorily address those reviews
   - patient advocate
   - originating scientific committee
   - others as needed

**CONCEPT Flow**

1. Imaging Co-PI is involved in concept development
2. Assumes Imaging Co-PI takes advantage of EDDS team to flesh out imaging objectives
3. CONCEPT DEVELOPMENT-IMAGING form would be signed by the primary imaging collaborator
4. IMAGING COMPONENT is defined as integral or integrated imaging, central archive, or central review, QC, or credentialing.
5. Imaging Science Advisory Committee (ISAC) review
6. Executive Review Committee (ERC) Imaging members review prior to formal ERC review.

**PROTOCOL Flow**

1. Imaging Co-PI | Imaging Co-PI
2. CONCEPT Finalization
   - Letter generated by Therapy PI
   - Imaging form signed by Imaging PI
3. CONCEPT has Imaging Component?
4. Project INDEX
5. ISAC CONCEPT Review
6. No CONCEPT Imaging Component (e.g., SOC > IROC)
7. ERC Imaging CONCEPT Pre-Review
8. ERC CONCEPT Review
9. No CONCEPT Review
Qualification Utility for the Imaging Core Laboratory (QUIC)

- Web-based tool developed by ACR (American College of Radiology)
- Efficient means for qualification process and communicating with EA and ACR core lab
- Site personnel can
  - complete the online scanner qualification
  - upload images
  - track the review process
  - get information on a scanner’s qualification expiration

QUIC – PET Trials
**NCI Molecular Analysis for Therapy Choice (MATCH) Trial EAY131**

- Analyzes patients’ tumors to determine for genetic abnormalities using a ‘basket’ or ‘umbrella’ approach
- Is there a targeted drug (i.e., an ‘actionable mutation’)?
- Assigns treatment based on the abnormality
- Each treatment is used in a unique arm
- Trial opened Aug 2015 with 10 arms
- Reopened May 2016 with 24 treatment arms
- Each arm expected to enroll a max of 35 patients
- Eligibility: solid tumors and lymphomas not responding to standard therapy

**NCI-MATCH Patients and Sites**

- 795 patients enrolled for screening in the first 3 months
- Far surpassing original estimate of 50/month
- Plan to enroll 5,000 patients
  - 192 active sites
    - (at least 1 patient)
    - 2/3 community
    - 1/3 academic
  - 796 approved sites

**MATCH Trial Flow**
**MATCH Trial Flow for imaging**

1. **Pre-enrollment Imaging**
2. **Biopsy Imaging**
3. **Refractory tumor**
4. **Enroll**
5. **Biopsy & mutation analysis**
6. **Actionable mutation?**
7. **Yes**
   - **Treat with study agent**
8. **SD**
9. **PR**
10. **CR**
11. **PD**
12. **PD**
13. **Biopsy & mutation analysis**
14. **Yes**
15. **Additional actionable mutation?**
16. **Yes**
17. **3 year followup**
18. **Off trial**
19. **no**
20. **Off trial**
21. **Biopsy & mutation analysis**
22. **no**
23. **Off trial**
24. **3 year followup**

**STUDY MODALITIES**

- **CT**
- **US**
- **PT**
- **MR**
- **NM**
- **CR**

*data as of 21 Sept 2016

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18F-Fluciclovine PET/CT in Patients With Rising PSA After Initial Prostate Cancer Treatment (LOCATE)

- **LOCATE** is a multi-center trial assessing impact of 18F-fluciclovine PET imaging in patients with rising PSA after initial prostate cancer treatment
- The utility of 18F fluciclovine PET/CT imaging is assessed by changes in treatment plan
- In May 2017, the study completed enrolment. More info at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT02680041)
- 18F-fluciclovine image interpretation is primarily qualitative, with increased uptake suspicious for prostate cancer recurrence
- We were able to add reconstructions with and without PSF to the LOCATE study to evaluate the impact
Including a model of the non-stationary detector point-spread-function (PSF) in image reconstruction

In principle can remove detector blurring

QIBA Profile precludes PSF-based reconstruction in measuring SUV

**Claim 1**: SUVmax is measurable from FDG-PET/CT with a within-subject coefficient of variation of 10-12%

**Claim 2**: A measured increase in SUVmax of 39% or more, or a decrease of -28% or more, indicates that a true change has occurred with 95% confidence

"... we note that this Claim should be reassessed for technology changes, such as PSF (point spread function) based..."

Recovery coefficient independent of target/background (T/B) ratio

Recovery coefficient dependent on T/B ratio

Courtesy of Dr. Martin Lodge, Johns Hopkins University
Process for Site qualification and Patient images

Qualification
- 18F Water-filled Uniform Phantom
- ACR PET Phantom
- many other details...

Image Reconstruction
- Time of Flight (TOF) reconstruction should be used
- PSF reconstructions should NOT be used for phantom images or patient interpretation
- However, sites were requested to provide PSF reconstructions of patient scans if they could

Sites / scanners

- Adler Institute
- Cedars Sinai
- City of Hope
- Fox Chase
- Genesis
- Huntsman
- Siemens Biograph 64 mCT
- Siemens Biograph 40 mCT
- Siemens Biograph 20 mCT
- Siemens Biograph 16 Truepoint
- Siemens Biograph

- PCMI
- Sand Lake
- Thomas Jefferson
- U Florida
- U Louisville
- U Penn
- GE Discovery IQ
- GE Discovery ST
- GE Discovery STE
- GE Discovery 710
- Philips Ingenuity TF

- Lenox Hill
- Liberty Pacific
- Loyola
- Mount Sinai
- Indianapolis VA
- Wash U

- 18 sites
- 20 scanners

Results
- 7 sites (9 scanners) performed PSF-based reconstructions
- 209 total subjects accrued

- 125 non-PSF
- 84 PSF
20 cm diameter Phantom
Example from qualification submissions for same scanner

ACR Phantom
Examples from qualification submissions for same scanner

Patient image 1/2

TOF
SUV Max: 10.3
SUV Mean: 7.8
SD: 1.8

TOF+PSF
SUV Max: 13.1
SUV Mean: 10.5
SD: 2.6
Patient image 2/2

**TOF**
- SUV Max: 11.1
- SUV Mean: 4.6
- SD: 1.9

**TOF+PSF**
- SUV Max: 15.6
- SUV Mean: 4.8
- SD: 3.0

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**Locate Trial Summary**

- Including a model of the PSF in image reconstruction is an appealing approach to improve resolution
- However, PSF causes bias and variance in SUVs
- This will increasingly be a challenge for clinical trials and clinical studies using SUVs
- Roughly 40% of studies could be collected with and without PSF-based reconstruction
- The LOCATE study showed that with careful trial planning, images could be collected without PSF
- Checking all images/headers for PSF is necessary

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**Imaging Core Lab Summary**

- Complex environment with multiple constraints
  - cost
  - patience & engagement by imaging sites: technologists, physicians, local physicists (if any)
- Many potential roles for medical physicists
  - non-standard of care protocols
  - trial design
  - qualification process
  - execution of the trial
Phantom measurements of ringing artifact

Bai, 2010 IEEE MIC conf record