Imaging Trials: ECOG-ACRIN

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Disclosures
- Research grant from GE Healthcare
- Co-Founder PET/X LLC

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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DRAFT GUIDANCE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

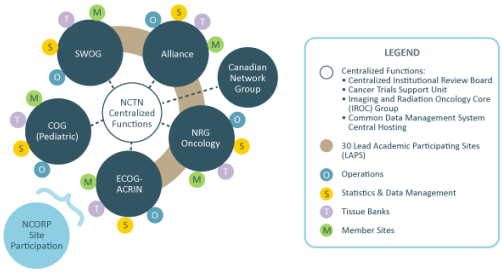
Revision 1

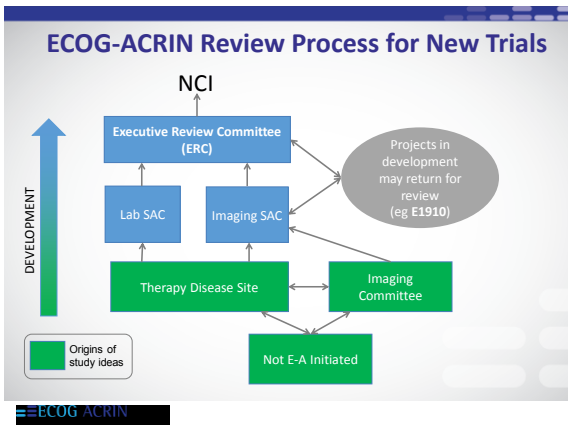
FDA Draft Guidance (paraphrased)

- 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)



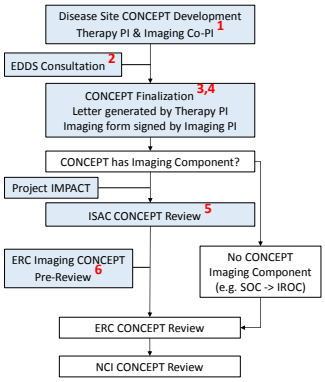


Imaging Science Advisory Committee (ISAC)

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

version September 27, 2013
ratified October 29, 2013

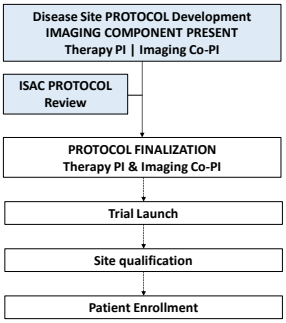
ECOG ACRIN



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.

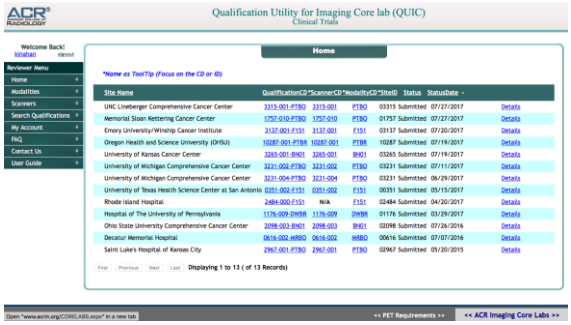
PROTOCOL Flow



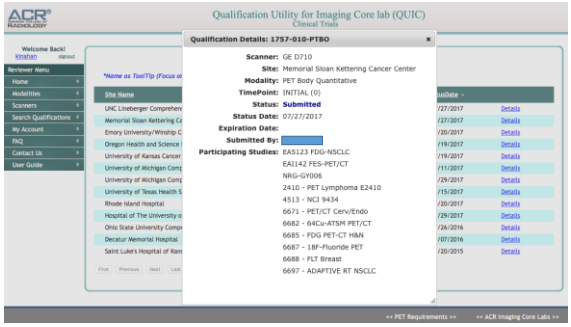
Qualification Utility for the Imaging Core Laboratory (QUIC)

- 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



QUIC – PET Trials

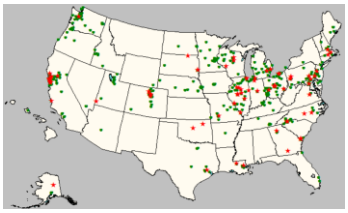


NCI Molecular Analysis for Therapy Choice (MATCH) Trial EAY131

- 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

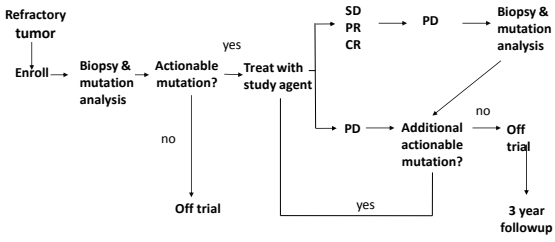
NCI-MATCH Patients and Sites

- 795 patients enrolled for screening in the first 3 months
- Far surpassing original estimate of 50/month
- Plan to enroll 5,000 patients

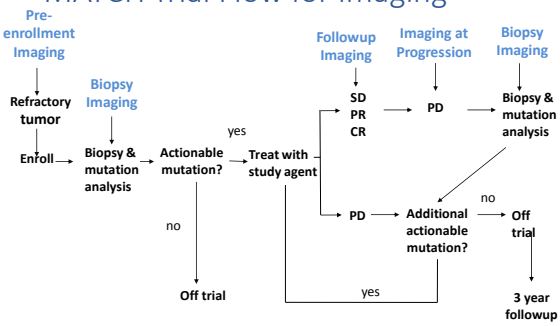


- 192 active sites (at least 1 patient)
  - 2/3 community
  - 1/3 academic
- 796 approved sites

MATCH Trial Flow



MATCH Trial Flow for imaging



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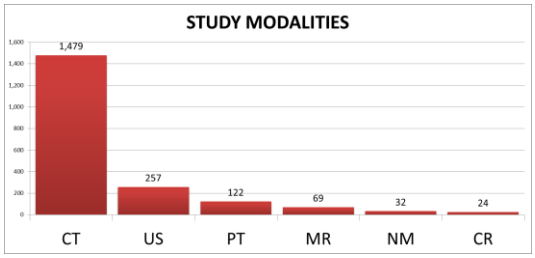
04/26/2016



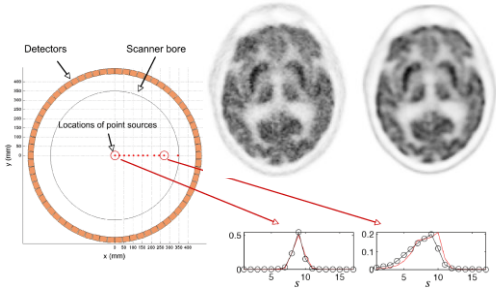
*data as of 21-Sept-2016

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

- LOCATE is a multi-center trial assessing impact of ^{18}F-fluciclovine PET imaging in patients with rising PSA after initial prostate cancer treatment
- The utility of ^{18}F fluciclovine PET/CT imaging is assessed by changes in treatment plan
- In May 2017, the study completed enrolment. More info at www.clinicaltrials.gov (NCT02680041)
- ^{18}F-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

Tong IEEE TNS 2011

QIBA Profile precludes PSF-based reconstruction in measuring SUV

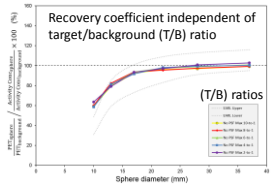
Claim 1: SUVmax is measurable from FDG-PET/CT with a within-subject coefficient of variation of 10-12%

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

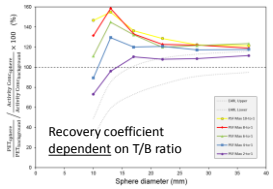
"... we note that this Claim sh
assessed for technology chan
(point spread function) based

Quantitative Imaging Biomarkers Alliance RSNA

No-PSF



PSF



Courtesy of Dr. Martin Lodge, Johns Hopkins University

Process for Site qualification and Patient images

Qualification

- 18F Water-filled Uniform Phantom
- ACR PET Phantom

Required to submit without PSF

+ 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	PCMI	Lenox Hill
Cedars Sinai	Sand Lake	Liberty Pacific
City of Hope	Thomas Jefferson	Loyola
Fox Chase	U Florida	Mount Sinai
Genesis	U Louisville	Indianapolis VA
Huntsman	U Penn	Wash U

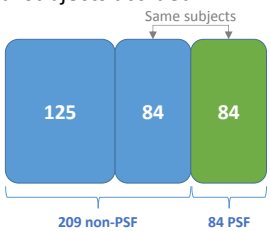
18 sites

Siemens Biograph 64 mCT	2	GE Discovery IQ	1
Siemens Biograph 40 mCT	5	GE Discovery ST	1
Siemens Biograph 20 mCT	1	GE Discovery STE	3
Siemens Biograph 16 Truepoint	1	GE Discovery 710	2
Siemens Biograph	2	Philips Ingenuity TF	2

20 scanners

Results

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

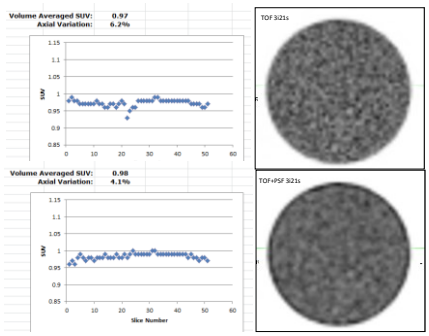


20 cm diameter Phantom

Example from qualification submissions for same scanner

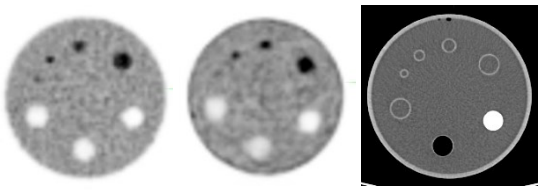
Time of flight without PSF (TOF)

Time of flight with PSF (TOF+PSF)



ACR Phantom

Examples from qualification submissions for same scanner

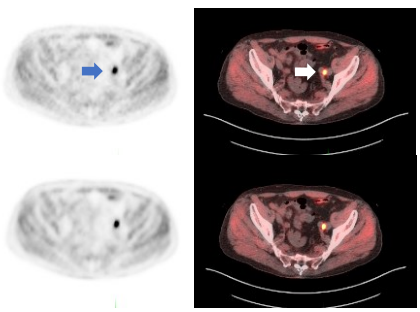


PET without PSF | PET with PSF | CT

Patient image 1/2

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

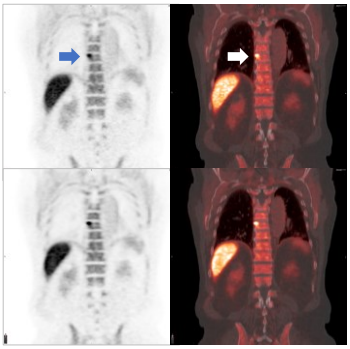
TOF+PSF
SUV Max: 13.1
SUV Mean: 10.5
SD: 2.6



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



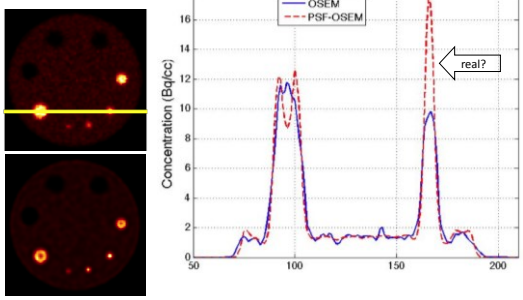
Locate Trial Summary

- 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

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