



Facilitating the Use of Imaging Biomarkers in Therapeutic Clinical Trials

Michael Graham, PhD, MD
President, SNM
Co-chair, Clinical Trials Network

Facilitating the Use of Imaging Biomarkers in Therapeutic Clinical Trials

- Definitions
 - Biomarker, Surrogate Biomarker
- Standardization
- Harmonization
- Elements of a clinical trial
- What can be facilitated
- SNM Clinical Trials Network

Imaging Biomarkers

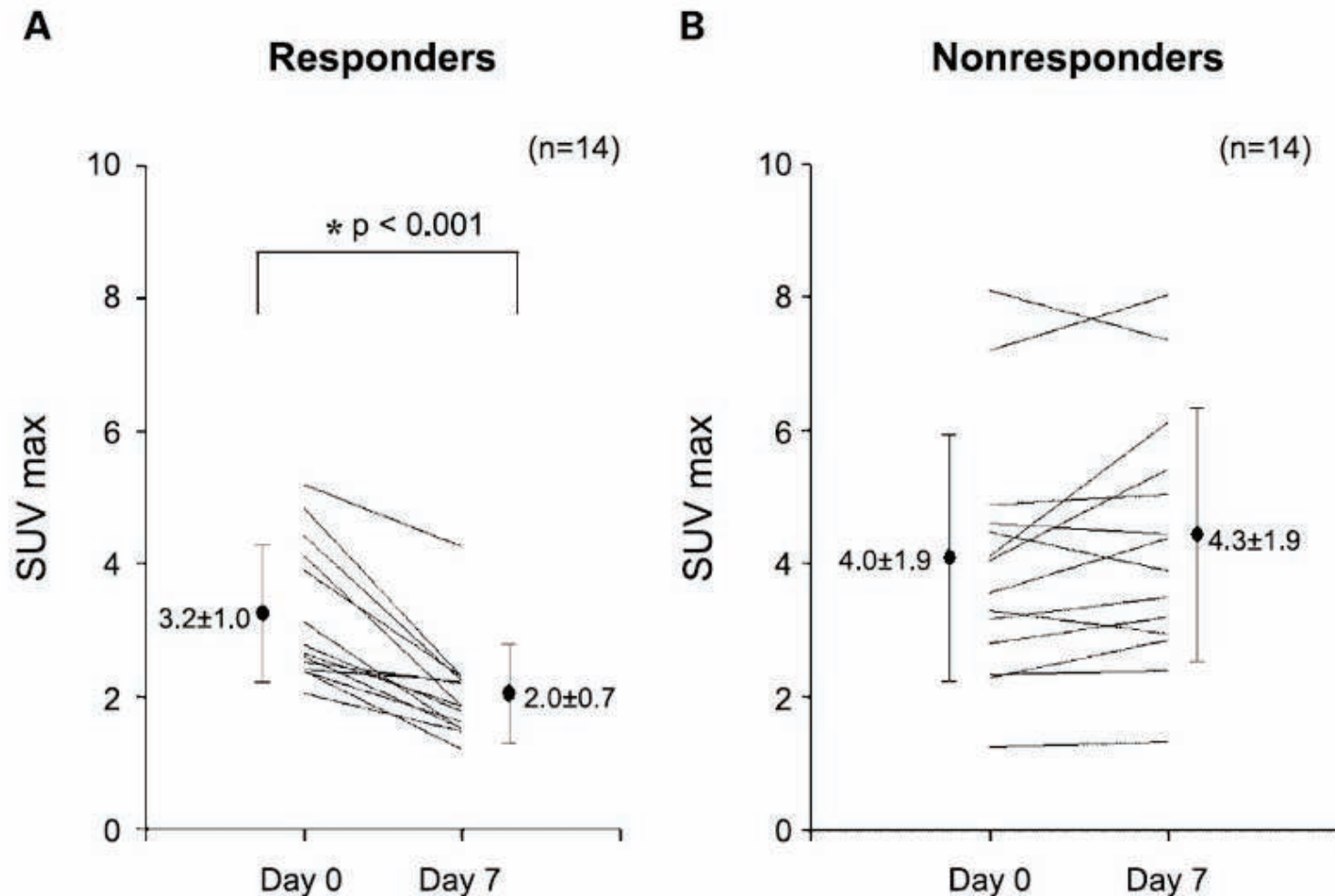
A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. (FDA website)

- Utility of imaging biomarkers in clinical trials
 - Assessing response to therapy (surrogate end point)
 - FDG
 - FLT
 - Stratifying patient populations
 - Receptor status (FES, SRS, etc.)
 - Hypoxia

Surrogate Endpoints in Clinical Trials

A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence. (FDA website)

- Assessing response to therapy
 - Relatively early “go vs. no go” decisions in Phase I or II
 - Decision point in adaptive designed trials
 - Building evidence for “validation” or “qualification”
- Personalized medicine
 - Early identification of responders and non-responders



Imaging
at 1 hr p
15 mCi
FLT

Threshold: decrease of $>10.9\%$ in SUVmax.

PPV & NPV were both 92.9%.

Facilitating the Use of Imaging Biomarkers in Therapeutic Clinical Trials

- Make sure the imaging biomarker is available
- Ensure that the biomarker is identical at all sites
- Ensure that the data collection is standardized
 - Patient preparation, device calibration, imaging protocol, reconstruction
- Ensure that the data analysis is standardized
- Ensure that the imaging data can be harmonized at the end of the study

Standardization involves the consistent performance of imaging, and adherence to protocols, for every research imaging study performed at a given clinical site.

Harmonization involves the identification and implementation of mechanisms to control for inconsistencies of data between the different sites, particularly to ensure that images taken and data generated with different tomographic systems are comparable.

Imaging Biomarker Availability

- Approved agents. e.g., Fluorodeoxyglucose
 - Can we assume all FDG is the same?
 - Is an IND needed?
- Investigational agents e.g., FLT, FMISO, PIB
 - Manufactured under an IND
 - If done under many different INDs, harmonization is more difficult
 - Pros and Cons of a single IND

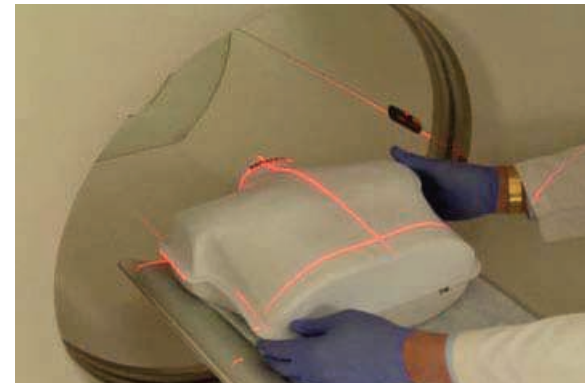
Imaging Standardization

- Protocol design should involve imaging experts
- Sites need to demonstrate they have the necessary infrastructure
- Sites need to demonstrate their capability to collect high quality data (examples & phantom assessment)
- Site personnel need explicit instruction in how to conduct the imaging part of the study
- Images (and associated data) need to be audited, especially early in the study



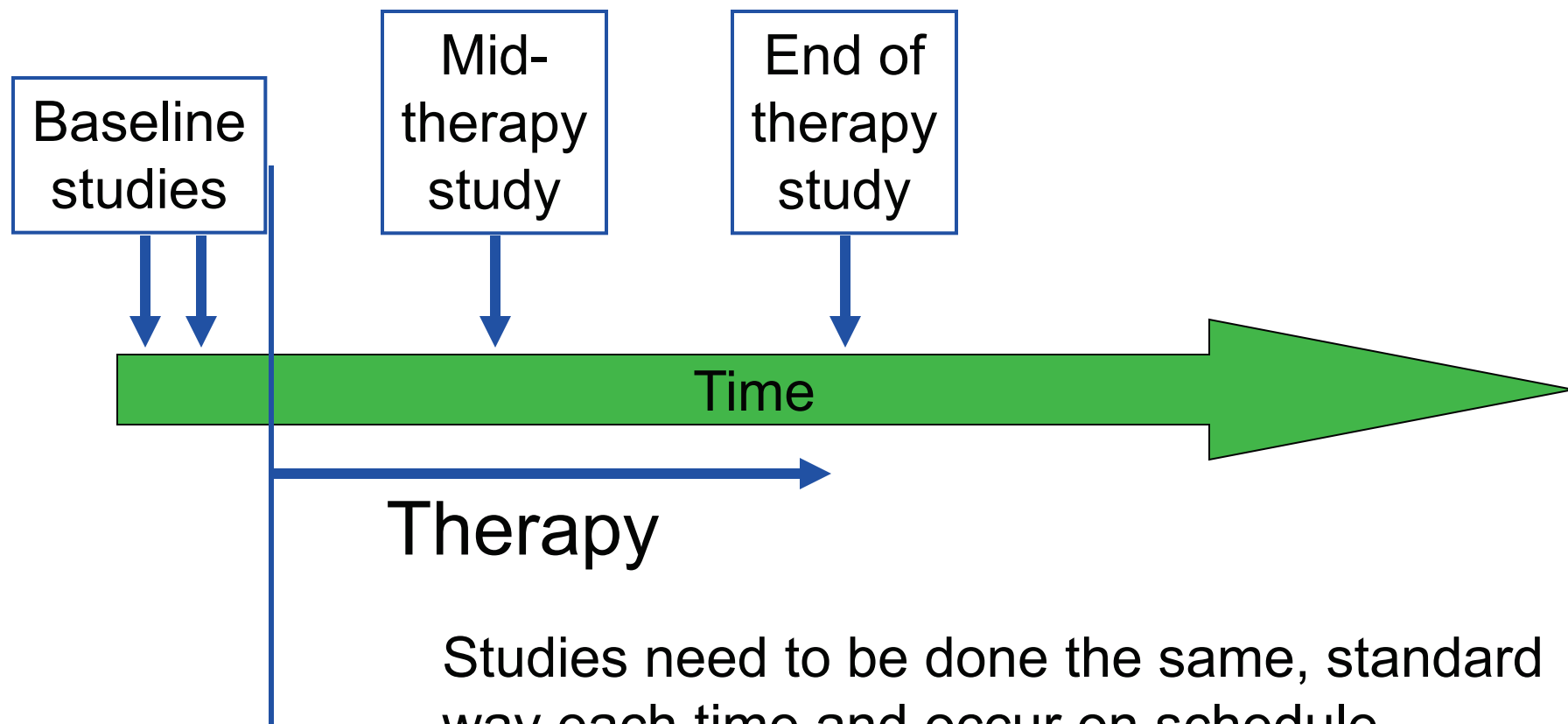
Oncology chest phantom & scan with mock lesions

All images courtesy of Paul E. Christian



Placing the chest phantom into the scanner

Typical Protocol



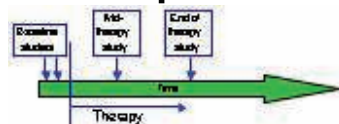
Studies need to be done the same, standard way each time and occur on schedule.

If not, this is a protocol violation, and the data may be unusable.

Sequence of Events

Setting: Company with a new therapy agent that is thought to be active against a specific type of tumor, ready for a Phase II trial

- Determine optimal imaging biomarker to use
- Determine numbers of patients and numbers of sites
- Identify sites with right patient populations and capabilities
- Identify manufacturing sites for the biomarker
- Qualify the sites
- Initial training of site personnel
- Initiate study
- Audit imaging and other data quality during trial
- Harmonize data
- Analyze data



ID BM
Pt numbers
Num of sites
ID sites
ID manufac
QA sites
QA manufac
Train sites
Trial
Audit
Harmonize
Analyze

Clinical Trials Network

- Provide a standardized imaging protocol for each agent that can be used across different trials
- Develop a group of pre-qualified sites capable of doing such trials
- Identify a group of pre-qualified manufacturing sites to provide the biomarker imaging agent
- Provide the capability of monitoring imaging quality during the trial
- Assist in the harmonization of imaging data at the end of the trial

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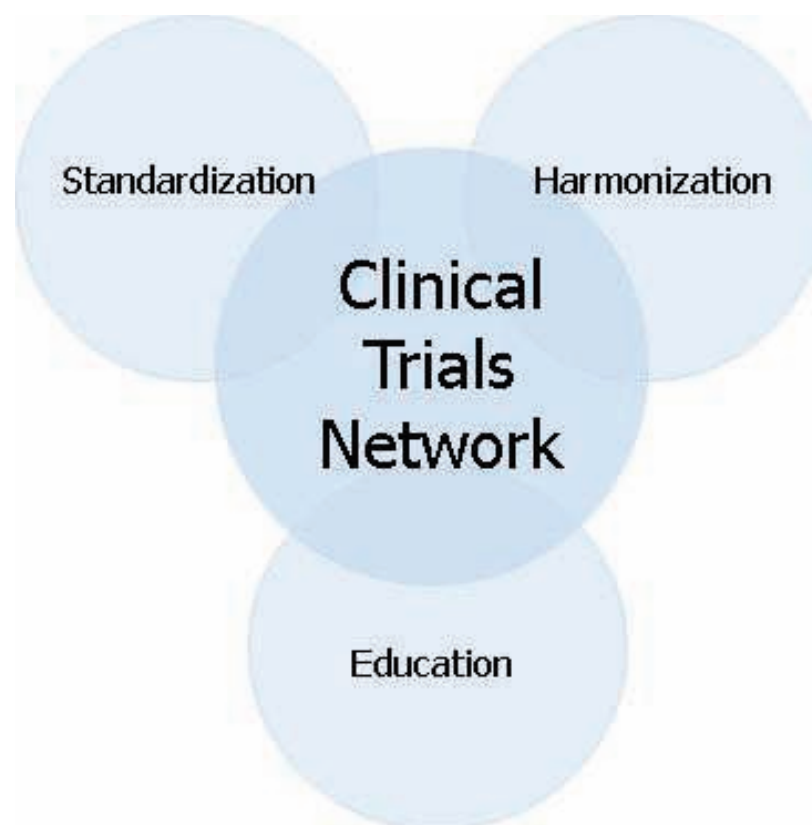
Clinical Trials Network: Mission

- Facilitate development of new imaging biomarkers
- Generate centralized imaging INDs
- Gather critical safety and efficacy – required by FDA
- Standardize radiopharmaceutical manufacturing/supply
- Coordinate standardized/harmonized imaging protocols
- Identify a group of pre-qualified imaging sites and biomarker manufacturers
- Provide ongoing education for investigators and technologists: imaging in clinical research trials

Promoting the Practice of Clinical Trials

Collaborating globally with:

- Radiopharmaceutical Manufacturers
- Drug Developers
- Pharmaceutical Industry
- Imaging Centers
- Regulatory Agencies
- Imaging CROs
- Other societies



CTN Defined Programs

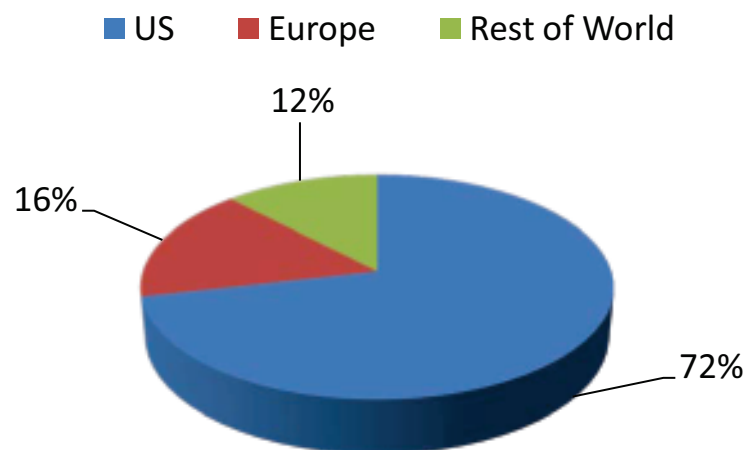
- Imaging Site / Biomarker Manufacturer Registries
- Scanner Validation via SNM Phantom Program
- Imaging Site Qualification and Monitoring
- Molecular Imaging Personnel Research Training
- Centralized IND



CTN Registries (April 2010)

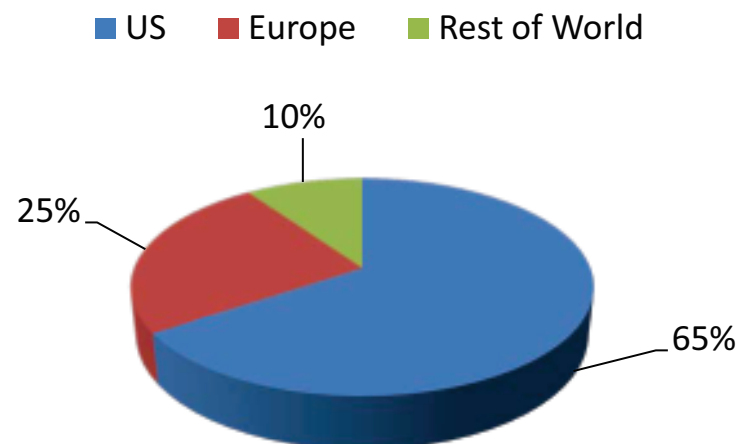
Consistent Interest and Growth

Imaging Site Registry (238 Sites)



April 2010

Manufacturer's Registry (206 Sites)



April 2010

Scanner Validation

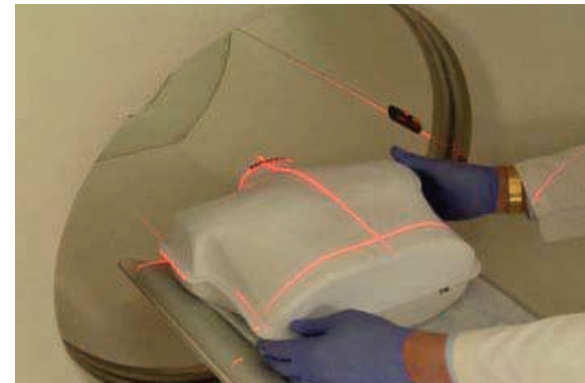
Sites scan the CTN PET chest oncology phantom (clinical simulator) to:

- Standardize imaging equipment
- Provide QA/QC data
- Serve as a prestudy “reader calibration” tool



Oncology chest phantom & scan with mock lesions

All images courtesy of Paul E. Christian



Placing the chest phantom into the scanner

Training and Education

CTN recognizes key role of molecular imaging technologists in promoting and improving imaging in clinical research studies

Curriculum courses offered for all imaging site personnel:

- Following clinical research imaging protocols
- Improving image quality / troubleshooting
- Monitoring QC and QA: equipment and imaging procedures
- Source documentation and CRF completion
- Regulatory requirements in clinical research
- Accurate documentation and reporting of violations, deviations and AEs/SAEs



CTN Accomplishments

- First SNM multicenter IND for an investigational imaging biomarker
- First three founding members from Pharma are on board
- 200+ members in both the imaging site and manufacturers registries;
- More than 25% participation in CTN from outside the U.S.
- International clinical oncology chest phantom program for scanner validation underway; 20 phantoms distributed globally
- Many ongoing educational activities in place and being developed

CTN Long-term Vision

- Expand multicenter IND capability for imaging biomarkers
- Promote molecular imaging in clinical trials; reach beyond PET biomarkers
- Expanded phantom program to include cardiac and brain indications
- Assist with protocol development using imaging biomarkers to improve standardization in imaging acquisition and processing