Harmonized PET Reconstructions for Cancer Clinical Trials

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## PET Imaging in Cancer Clinical Trials

<table>
<thead>
<tr>
<th>Clinicaltrials.gov identifier</th>
<th>Sponsor</th>
<th>Endpoint</th>
<th>Imaging Endpoint</th>
<th>Title</th>
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<tr>
<td>NCT00098605</td>
<td>GSK</td>
<td>Secondary</td>
<td>[18F]FDG-PET metabolic response</td>
<td>A Phase II Trial of GW572016 For Brain Metastases in Patients with HER2-Positive Breast Cancer</td>
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<td>NCT00320385</td>
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<td>Lapatinib In Combination With Trastuzumab Versus Lapatinib Monotherapy In Subjects With HER2-positive Metastatic Breast Cancer</td>
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<td>[11C]Lapatinib-PET PK</td>
<td>Exploratory Lapatinib (Positron Emission Tomography) PET Study in Subjects With Breast Cancer</td>
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<td>Pfizer</td>
<td>Primary</td>
<td>[18F]FLT-PET proliferative response</td>
<td>A Pilot Study Of PD-0332991 In Patients With Previously Treated Mantle Cell Lymphoma</td>
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<td>Regorafenib in Patients With Metastatic and/or Unresectable Gastrointestinal Stromal Tumor</td>
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<td>NCT00459186</td>
<td>Novartis</td>
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<td>The Use of RAD001 With Docetaxel in the Treatment of Metastatic, Androgen Independent Prostate Cancer</td>
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<td>Bevacizumab Plus Ipilimumab in Patients With Unresectable Stage III or IV Melanoma</td>
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<td>A Phase 1 Study of BMS-833923 (XL139) in Subjects With Advanced or Metastatic Cancer</td>
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<td>Neoadjuvant and Adjuvant Imatinib Mesylate in Treating Patients With Primary or Recurrent Malignant Gastrointestinal Stromal Tumor</td>
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</table>

PET imaging is inherently quantitative, and well suited for use in cancer clinical trials with imaging endpoints.
Challenges:

- Substantial variability in PET image quantitative accuracy hampers its use in multi-center trials

  This signal source size- and PET scanner-dependent variability

- Degrades the quality of clinical trials by requiring more patient accrual (to reach statistical significance in clinical trials)

- Leads to inconclusive results in tests of badly needed cancer therapies
Impact of Different Reconstructions on Objects of Different Sizes

Even in the same scanner, substantial quantitative differences are seen depending upon the chosen reconstruction parameters.
Impact of Quantitative Variability on Sample Size in Clinical Trials

Reducing inter-scanner reconstruction and calibration variability (Goals of the grant) by 10% (for example from 30% to 20%) can lead to a decrease in necessary sample size of a factor of two or more in a clinical trial.

Project Overview

- Designed to reduce quantitative variability of PET image data in clinical trials through identification and verification of quantitatively harmonized reconstructions.

- True Academic industrial partnership with
  - Industry scientists as true co-investigators (funded by industry)
  - Management buy-in to implement results of project in commercial product (if successful)

- Long-term project sustainability through built-in engagement of professional organizations and societies.
  - SNMMI/CTN, RSNA/QIBA
Industry and Society Involvement

The Clinical Trials Network (CTN) of the SNMMI is coordinating the project, providing administrative support for the considerable logistics, and contributing necessary image server and software infrastructure.

GE, Philips, and Siemens are each contributing access to their physics and engineering leadership for scientific collaboration, while also contributing personnel and hardware infrastructure necessary to perform the controlled image reconstructions for the project.

NIST is providing expertise associated with the $^{68}\text{Ge}^{68}\text{Ga}$ NIST traceable sources used in this project. Rad-Qual is manufacturing the NIST traceable sources used in this project.

EANM Research Limited (EARL) is collaborating to assure that harmonization efforts associated with this project are performed as much in concert with parallel efforts by EANM as possible.

RSNA and its QIBA initiative and association with ACR’s ACRIN provide a long-term sustainability mechanism for project results.
Industry Buy-In

○ Top PET imaging scientists from Siemens, GE and Philips to help with identifying make and model specific reconstruction parameters to be harmonized to result in PET images quantitatively identical to one another for use in clinical trials.

○ The Industry Partners have agreed that pursuit of identification of make and model specific harmonized reconstruction parameters to use only in clinical trials is a non-competitive space in which direct involvement is globally beneficial to the molecular imaging field.

○ Vendor scientists are actively engaged in this project. They are responsible for:
  – Performing version controlled reconstructions (from acquisition date provided for academic sites) for all of their scanner models for the project
  – Providing scientific guidance on the project
  – Industry scientists are full partners in this project.

Very specific commitments and action plans from industry partners
1. Identify (with help of vendors) all recent and current make and model PET/CT scanners (currently 13)
2. Image the NEMA Imaging Quality IEC Phantom with a spectrum of sphere sizes on each scanner model.
(take data from scanners of each model from 2 different imaging sites)
3) Generate Recovery Coefficient Curves for spheres of different sizes for each scanner, and over a broad range of reconstruction parameters.
4) Identify harmonizable regions in the set of Recovery Coefficient curves into which all subsequent harmonized reconstructions will reside.
Harmonized PET Reconstructions for Cancer Clinical Trials

Take Home Message

- Potential for significant improvement to multicenter cancer clinical trials
- Wide and specific participation by industry and research communities, planning for long term sustainability
- Potential implication in addressing Big Data challenges