BREAKOUT SESSIONS

- **Breakout Session #1**
  - Imaging Overview
    - DAT Scan Imaging
    - MRI

- **Breakout Session #2**
  - Biologics Overview
    - Kits and Supplies
    - Specimen collection, processing, storage, and shipment

- **Breakout Session #3**
  - Lumbar Puncture
    - Purpose of LP
    - Process and Procedures
    - Helpful Hints
Overview of DaTSCAN Imaging Logistics

John Seibyl, MD
Susan Mendick, MPH
Institute for Neurodegenerative Disorders, New Haven, USA
Practical Issues in Large Imaging Clinical Trials

- Subject recruitment

- Coordination between clinical and nuclear medicine groups

- Regulatory and licensure issues

- Technical issues - need for standardization to create poolable imaging datasets despite different cameras, acquisition and processing protocols
Technical Challenges in Multicenter Imaging Trials

- Different cameras have different physical characteristics
- Image reconstruction and filtration
- Algorithms for scatter correction, managing randoms
- Post hoc processing: attenuation correction, spatial normalization,
- VOI strategies
- Normal controls: what’s normal, how heterogeneous
- Camera drifts, especially over long studies
- Other sources of increased variance:
  - updates in reconstruction
  - software
  - ambient changes in background radiation levels,
  - inadvertent nearby radiation sources (patients, syringes, etc.)
Factors Which Influence the Striatal Binding Ratio

- **Biological factors**
  - Dopamine transporter density
  - Age
  - Pharmacokinetic factors- rate of uptake, metabolism and elimination of tracer
  - Genetic: allelic variants of DAT
  - Drugs competing with DATScan for DAT binding
  - Patient ability to remain motionless in the camera

- **Technical factors**
  - Equipment: Resolution and sensitivity of selected camera, collimator
  - Performance drifts over time
  - Photon flux- counts in image
  - Reconstruction/filtration
  - Size and placement of regions of interest
Data and Information Flow in Imaging Studies

Study Site
Neurology/Psychiatry
Nuclear Medicine

ICL
Image quality assurance and review, processing, visual analysis,

LONI

CTCC
Imaging Core Lab (ICL) Responsibilities

- Assess site technical capabilities
- Perform SPECT technical site visits
- SPECT data:
  - QC data
  - Provide Visual Interpretation* (Screening only)
  - Analyze data
  - Provide data for inclusion in study database

* For confirming enrollment
ICL Responsibilities

- Structural MRI data
  - QC data
  - Provide data for inclusion in study database

- DTI MRI data
  - QC data
  - Prepare data for analysis
  - Provide data for inclusion in study database
Unique Technical Features of PPMI SPECT

- Use of 57Co striatal correction phantom scanned each time a PD patient is imaged
  - Corrects for camera differences and drift
  - Allows pooling of all data for standard comparison to normal healthy database

- Employment of objective image analysis including possibly automated algorithms

- Technical site set-up visit

- Ongoing image submission, review, and feedback
Technical Qualification Process

STEP 1  Technical Site Questionnaire

STEP 2  ICL core lab reviews technical characteristics of site

STEP 3  Transfer of de-identified test data to ICL

STEP 4  Imaging Qualification Visit scheduled with clinical and imaging teams

STEP 5  Image qualification visit: Meet with local site team, set up acquisition protocol, acquire brain phantoms, reconstruct, test send of data to ICL, review documentation procedures

STEP 6  Integrity of transferred data reviewed by ICL and ok to proceed given to site
Anthropomorphic Striatal Phantom for Set-up Calibration
<table>
<thead>
<tr>
<th>Test</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performed by each site within one month of initial subject enrollment</strong></td>
<td>Uniformity correction/ gain calibration</td>
</tr>
<tr>
<td>COR correction</td>
<td>Corrects image registration</td>
</tr>
<tr>
<td>Energy correction</td>
<td>Establishes energy correction</td>
</tr>
<tr>
<td><strong>Performed prior to subject enrollment by technical CRO</strong></td>
<td>[(^{123}\text{I})] distributed source phantom</td>
</tr>
<tr>
<td>[(^{123}\text{I})] Striatal phantom</td>
<td>Allows baseline measure for evaluation and comparability of recons, region sampling, etc</td>
</tr>
<tr>
<td>(^{57}\text{Co}) striatal phantom</td>
<td>Determines a correction factor for cross-camera calibration of specific:nonspecific uptake ratio</td>
</tr>
<tr>
<td><strong>Performed during study each day a protocol subject is scanned</strong></td>
<td>(^{57}\text{Co}) striatal phantom</td>
</tr>
<tr>
<td>Routine SPECT and dose calibrator QC</td>
<td>Maintains integrity of camera and dose calibrator</td>
</tr>
</tbody>
</table>
Good Imaging Practices (GIP)
Technical Binder

• Provided at technical set-up

• Contains:
  • Core lab contact information
  • Technical operations manual
  • Imaging source documents
  • Image data transfer documents
  • Imaging day and file transfer checklists
  • Technical correspondence log
  • Examples of completed documents
Dual Energy Window Acquisition Protocol for both 57Co phantom and PD patient

Co-57 photopeak

I-123 photopeak
57-Co Striatal Phantom

mid-brain

2 striata

 occipital
Use of Phantom to Correct PD Data

- Phantom should be acquired each day a PD patient is imaged
- Patient data will be analyzed before and after “correction” by phantom
Factors Which Influence the Striatal Binding Ratio

- **Biological factors**
  - Dopamine transporter density
  - Age - *Within subject measure*
  - Pharmacokinetic factors - rate of uptake, metabolism and elimination of tracer
    - Adherence to protocol for imaging time post injection
  - Genetic: allelic variants of DAT – *Within subject measure*
  - Drugs competing with DATScan for DAT binding
    - History and subject screening
  - Patient ability to remain motionless in the camera
    - Education, encouragement, and support

- **Technical factors**
  - Equipment: Resolution and sensitivity of selected camera, collimator
    - Single camera for study for which phantom data obtained, 57Co correction
  - Performance drifts over time - track with QA log, use correction phantom
  - Photon flux - counts in image - correct injected dose, imaging time
  - Reconstruction/filtration - adherence to pre-established tech parameters
  - Size and placement of regions of interest - automated image processing
DaTSCAN SPECT Imaging
Imaging Day Activities

- $^{57}\text{Co}$ phantom acquisition
- Urine pregnancy test for women of childbearing potential
- Administration of thyroid protection prior to injection
- 5 mCi (+/- 10%) DaTSCAN Injection
- SPECT acquisition 4 hours (+/- 15 minutes) post injection
- Adverse event assessment during imaging day and 7 days (+ 3 day) telephone call
Imaging Protocol

- Bolus injection of 185 MBq
- Imaging commencing at 4 h (±15 m) post injection - very important!
- 20% symmetric energy window centered on 159 keV
- 20% symmetric energy window centered on 122 keV
- 128 x 128 matrix, parallel hole or fanbeams
- 3 degree angular sampling with heads within 15 cm radius
Post Imaging Visit Activities

- Completion of ICL documents
- Timely transfer of imaging data ($^{57}$Co phantom, raw and reconstructed SPECT data) to core lab
- Screening SPECT to be transferred to ICL within 24 hours of acquisition
Imaging Source Documents
SPECT Scan Information Source Document

- Data on form includes:
  - Subject data
  - Pre-injection data
  - Injection data
  - Scan acquisition information

- Make sure all fields are completed.
- Confirm correct subject ID is recorded.
Data recorded on form includes:
- Scan Identifiers and number of projections/slices

Site must:
- Confirm that the number of the projections/slices recorded on this form matches the actual number sent
- Use correct scan identifier
Camera QA Event Log

- Purpose of form:
  - to record daily camera QC (including new flood tables, camera service, software updates, preventative maintenance, power outages, back-up camera use, etc.)
  - reviewed at ICL to see if anything was done to the camera that may affect acquisition
Source Document Completion

• General guidelines:
  • Complete all fields
  • Do not use “ “ marks
  • If you make a mistake, line through incorrect entry, initial and date change
  • If transcribing info from another source onto a core lab source, please double check transcription is correct
Query Process

- Source documents are reviewed for completeness and accuracy.

- Missing information/clarification needed results in issuance of a Data Clarification Form (DCF) to site.

- DCF’s are to be completed and returned to the ICL within 5 working days of receipt.

- Technical QC process is halted until DCFs are resolved.
Query Process

• Technical Issue Clarification Report (TIC Report)
  • Generated for issues that are more technical nature, (i.e. acquisition procedures, reconstruction procedures)
  • TIC reports are to be completed and sent back to ICL within 5 working days of receipt
  • Technical QC process is halted until TIC report is resolved
How to Avoid DCFs

• Most common reasons why site is queried:
  • Data is sent identified

  • Missing information on source documents (do not leave blanks or use “ “ marks in place of repetitive entries)

  • File number discrepancies
    • Recon parameters not following site set up acquisition protocol
    • Injected Dose does not equal initial assay less residual (decay has been applied?)
How to Avoid DCFs

- Disclose any information regarding the injection and scan acquisition if not completed per protocol
  - Examples:
    - high or low dose injected
    - camera had to be restarted
    - Possible subject motion

  Record in comments section of imaging source documents
Screening SPECT Visual Interpretation
Visual Interpretation

- A report will be generated for each screening SPECT scan
- Report will indicate either:
  - DAT scan is consistent with dopamine transporter deficit
  - DAT scan is consistent with no dopamine transporter deficit
Visual Interpretation

- PD subjects must have dopamine transporter deficit to be enrolled
- HC subjects must have NO dopamine transporter deficit to be enrolled
- Screening SPECT scans need to be transferred to the ICL within 24 hours of acquisition
DaTSCAN Ordering Process (for European Sites)
DATSCAN ORDERING PROCESS (Europe)

- DaTSCAN for will ordered through usual commercial suppliers
- Sites will be provided with a designated country representative from GE
- Supply details for each country will be provided
DaTSCAN Ordering Process (for U.S. Sites)
DaTSCAN Ordering Process (U.S.)

- Currently DaTSCAN is not an approved drug
- DaTSCAN is a schedule II drug
- Investigator responsible for ordering the DaTSCAN must hold a DEA license allowing schedule II drugs
- Shipping address for DaTSCAN must match address on DEA license
DaTSCAN Ordering Process (U.S.)

- Current days of week during which DaTSCAN is available is still being determined
- DaTSCAN can be ordered up to 12:00 CST two days prior to the imaging visit
- DaTSCAN order form to be submitted to the Institute for Neurodegenerative Disorders
- DEA Form 222 need to be submitted to GE
DEA Form 222 must be completed and submitted to GE.
MRI Acquisition
Typical technical parameters for T1 MRI

<table>
<thead>
<tr>
<th>Type of sequence</th>
<th>T1-3D (e.g. MPRAGE, SPGR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (ms)</td>
<td>5 – 11</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>-</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>1 – 1.5</td>
</tr>
<tr>
<td>Interslice gap (mm)</td>
<td>0</td>
</tr>
<tr>
<td>Voxel size (mm)</td>
<td>1<em>1</em>1.2</td>
</tr>
<tr>
<td>Matrix</td>
<td>256 x minimum 160</td>
</tr>
<tr>
<td>Plane</td>
<td>sagittal</td>
</tr>
</tbody>
</table>
Requirements for DTI-MRI

- DTI-MRI will be done at selected sites
  - Siemens
  - Trio
  - 3.0 Tesla Scanner
MRI Transmittal to ICL

- MRIs done during screening will need to be sent to ICL
- The MRI Transmittal form needs to be completed and sent with the MRI (faxed or e-mailed, if MRI is sent electronically, or included with the CD)
- CD’s must be labeled with Study protocol number, site #, Site name, and Subject Randomization number.
What happens to the data once it arrives at the ICL?

- Verify receipt of correct data and all of the correct paperwork
- Queries may be generated.
- Images undergo Technical Quality Control (TQC) and Scientific Quality Control (SQC) review
- Imaging Data Receipt Form is generated and sent back to the imaging center with a copy to the clinical coordinator.
  - Form is to be maintained in technical binder
  - For 1st subject data, receipt of this form back at the site indicates approval to proceed with enrollment
- For screening images only; visual interpretation provided to site
PPMI represents an important collaboration *between* international investigators across sites, but also *within* the multidisciplinary groups *within* a site to develop a unique set of PD biomarkers for the movement disorder community.

The logistics and choreography of this study from a core lab perspective are daunting, but doable.
PPMI Investigators Meeting
Biofluids Overview

Leslie M Shaw
University of Pennsylvania Medical Center
Qualification of the analytical and clinical performance of CSF $\text{A}_\beta_{1-42}$, tau and $p$-tau$_{181p}$ in the ADNI study

1. Selection of CSF $\text{A}_\beta_{1-42}$, tau, $p$-tau$_{181p}$ based on prior studies that showed their promise for AD detection & a consensus among experts in this field

2. Pre-analytical factors for the lp & CSF handling
   Identify and control for pre-analytical variables
   - Time of day for lp - *morning following overnight fast*
   - Collection tube type - *avoid PS and glass tubes & use PP tubes*
   - Transport temperature - *avoid storage at refrigerator temp*
   - # of freeze-thaw cycles - *minimize*
   - Time from collection to freezing - *minimize*

3. Analytical performance
   Assure stability of reproducibility of test performance
   - Within each run
   - Day to day
   - Among expert laboratories
   - From batch to batch of immunoassay reagents
   - AA-sponsored international CSF external blinded quality control program

4. Clinical diagnostic performance
   Establish diagnostic and predictive performance using the qualified test method
   - Establish sensitivity & specificity in ADNI-independent CSF samples from autopsy-confirmed AD subjects
   - Use these diagnostic cutpoints to characterize AD CSF pathologic biomarker signatures in ADNI subjects
   - Evaluate predictive performance for MCI→AD converters
   - Characterize the longitudinal changes in CSF biomarker changes in a subset of ADNI CSF donors
   - Study multiple biomarker types in combination for optimal disease detection and progression
Documentation of biofluid sample “history”

- Time/date
- Time to process
- Time to freeze
- Assess sample quality
- Accurate de-identified labeling
- 24/7 tracking of storage temp
- A critical part of the value of biofluids is documentation of pertinent pre-analytical factors that can affect biomarker measurements
CSF sample collection for ADNI:

- After overnight fast
- Collect into polypropylene tube
- Transfer to polypropylene transfer tube
- No centrifugation
- Freeze at site, ship on dry ice
- Thaw & aliquot at UPenn, storage at -80°C
ADNI CSF samples

Time from collection to transfer

CSF Samples
Time from Collection to Transfer

<table>
<thead>
<tr>
<th></th>
<th>CSF BL</th>
<th>CSF Yr1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>407</td>
<td>312</td>
</tr>
<tr>
<td>Mean</td>
<td>25.7 min</td>
<td>24.0 min</td>
</tr>
<tr>
<td>95% CI</td>
<td>22.2-29.2</td>
<td>19.8-26.2</td>
</tr>
</tbody>
</table>
The Future of Biomarker Research: Critical Goals

- Standardize CSF sampling / handling procedures
- Laboratory procedures
- Manufacture lot to lot consistency
- External control program
- Prospective studies:
  - Interrelationships between imaging and biochemical biomarkers in longitudinal studies
  - Longitudinal trajectories for transitions from cognitively normal → early MCI → late MCI → AD
  - Effect(s) of various treatment strategies on disease progression and biomarker measures
  - More biomarker study data on natural history of AD in the cognitively normal elderly population
- Approval for use in clinical practice
The Research Lumbar Puncture: CSF Biomarkers for Alzheimer’s Disease

Elaine R. Peskind, M.D.

Friends of Alzheimer’s Research Professor,
Department of Psychiatry and Behavioral Sciences
University of Washington School of Medicine

Associate Director
University of Washington
Alzheimer’s Disease Research Center

Co-Director, VA Northwest Network
Mental Illness Research, Education, and Clinical Center, Seattle, WA
Why CSF?

Pros and Cons

- Cons:
  - blood or urine most practical and acceptable
  - risk of adverse events

- Pros:
  - most reliable for assessing brain metabolism and function
  - limitations to interpreting blood or urine derived markers
  - perceived limitation of adverse events is not supported by evidence
CSF - Safety

- Sterile technique
- 24g Sprotte atraumatic spinal needle with 20g introducer
- 25g 1 1/4” Quincke needle for deep local anesthesia
- For thin subjects, don’t insert introducer or deep local anesthesia needle all the way
- Can safely draw up to 30 ml in most normal adults – small adults – draw more slowly to prevent acute frontal headache
- Post-LP precautions to minimize headache risk
Sprotte 24 g Spinal Needle
Adverse Events in Research Lumbar Puncture: All Subjects

- 428 lumbar punctures (age range 21-88)
- Post-LP headache:
  - epidural blood patch indicated: 0.9%
  - any headache: 6.8% (19/29 rated as mild)
- Back pain or soreness:
  - mild: 2.6%
  - moderate: 0.5%
- Vasovagal response: 0.9%
- Nausea: 0.7%
- Other: 0.2%
Adverse Events in Research Lumbar Puncture: AD Subjects Only

- 78 lumbar punctures
  - mild headache: 1
  - mild back soreness: 2
  - mild nausea: 1

- Any adverse event: 5%
  - all rated as mild

Adverse Events in Research
Lumbar Puncture

- Risk of post-LP headache unrelated to:
  - age
  - gender
  - position during LP
  - time of recumbent rest following LP
  - amount of CSF withdrawn up to 30 mls
  - diagnostic group - risk lower in AD/MCI patients

Mean (± SEM) anxiety and pain ratings immediately following lumbar puncture by subject group. One-way ANOVA revealed significant group effects for both anxiety and pain.

*anxiety ratings significantly higher in young subjects than in old or AD/MCI subjects, p<0.01.

**pain ratings significantly higher in young subjects than in old subjects, p<0.05.
CSF - Subject Acceptability Issues

- Sensitive and “matter of fact” presentation of lumbar puncture procedures
- Talk subject “through it” – no surprises
- Provision of adequate local anesthesia