YALE UNIVERSITY PET INVESTIGATORS GUIDE
December, 2015

This document contains information we would like to share with you concerning performing PET studies in the Yale PET Center. Please take a look at the information provided. In subsequent versions, we will add future topics, as listed below.

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Future topics:
- Adverse Events Policy
- Authorized User
- Suggestions for discussing PET scans with normal volunteers (e.g., radioactivity, arterial lines)/Subject Safety

Please refer general questions or comments to Richard Carson, Ph.D. (richard.carson@yale.edu).

Scheduling PET Scans

There are 3 components to scheduling PET studies.

- Initiating a new, approved protocol (form on page 27 required)
- Requesting scan slots (email notification required)
- Providing subject information before each scan (form on page 29 required)

Initiating New PET Studies/Protocols

Prior to initiating/scheduling a new, approved PET protocol you are required to complete and submit a Protocol Initiation Form (page 27) and provide the following information/ documentation to the PET Center scheduling address: PET.scheduling@yale.edu

Information Requested on Form:

- Name and contact information for Principal Investigator.
- Official protocol title and HIC or IACUC number. (Note: PET Center will also assign an abbreviated code name (aka "short name") to the protocol that will be used in communications.)
- Name and contact information of Research Assistant and/or Scheduler.
- If supplying your own medical/nursing/vet staff, include contact information.
- Number of subjects to be scanned.
- Expected start and end date of PET scanning.
- Approximate rate of scans (e.g., 1 scan per month)
- Scanner to be used: HRRT, HR+, mCT, Focus-220
- Pharmacologic Compound (i.e. cold non-radioactive drug), if applicable
- Number of scans per subject and any time/day restriction, if required. Examples:
    - 2 scans, 7 days apart, with both injections before 12 PM
    - 2 injections on one day with break of at least 90 min between scans
- PTAEO (with expiration date) for scan billing or name, email, and phone number of person responsible for billing
- PTAEO (with expiration date) for subject payment (if PET Center is issuing subject payments)
- Tracer Name
- Tracer Source (made by PET Center or purchased/delivered/expected time of delivery on scan day/contact information if purchased/delivered by outside source)
- Indicate whether metabolites, arterial lines, or PK samples are required
- Funding agency/mechanism

Required Documentation:

- Electronic copy of HIC or IACUC approval letter
- Electronic copy of approved protocol/all consents/PET Procedures Manual (industry scans)

- Y-NHH Radiation Safety Committee approval letter or Yale University RDRC approval letter (human studies) and FDA 2915 form (if applicable)
- Yale University Radiation Safety Committee approval letter
- PET Center must receive these documents before any scans will be scheduled.

Radiation Safety Training

PI's /RA's /Staff accompanying subjects to and from the PET Center for PET scanning are required to complete Radiation Safety Training (see training procedures on page 32)

Requesting PET Scan Slots

To request PET scan slots, please send an email notification to the PET Center scheduling address: PET.scheduling@yale.edu. *Do not* send emails to individual staff in the PET Center. Information needed:

- Protocol short name and HIC number in subject line of email (tracer name only is not sufficient)
- Number of slots required and of what type
- Specify one scan only, or ongoing request (e.g., 2 per month)
- Range of dates and times
- Special requirements

Providing Subject Information

Once your slots are defined, please complete the PET Subject Information Form (page 29) and submit (along with a valid, signed consent) by email to PET.scheduling@yale.edu by 3PM, **3 business days before the scheduled study date**, otherwise scans may be cancelled (at the discretion of the PET Center staff) and cancellation fees will be applied. We require this information to prepare our databases as well as to check on radiation dosimetry of human subjects.

IMPORTANT: For pharmacologic studies, those using cold (non-radioactive) drug in addition to radiotracer, RAs must provide subject medical records on day of scan (including laboratory and EKG results).

Subject information requested:

- Protocol short name
- HIC number
- PI name and phone number
- RA name and phone number
- PET Scan date
- Subject arrival time
- Legal first and last name
- Date of Birth
- Subject age at PET scan date
- MRI TR#
- Gender
- Ethnicity

- Diagnosis- primary and secondary
- Any current medications
- Known allergies
- Labs and EKG if study uses arterial line or pharmacologic compound (cold non-radioactive drug)
- Height & Weight
- Subject study ID
- Subject phone number
- Name of research staff accompanying subject
- Any pertinent health history and progress notes
- Request for vegetarian lunch
- Subject travel arrangements

Cancellation of PET slots

We have instituted the following steps in the weeks preceding each PET scan slot to facilitate communication and minimize the number and impact of scan cancellations.

Should a scan need to be cancelled, please identify the scan slot to be cancelled by the HIC number, PET short name, scanset ID number, and state the reason for cancellation.
A fee for late scan cancellations will be charged, as detailed below.

- Fourteen (14) calendar days before a scheduled scan slot, you will receive an email reminder that will include the date and number of scans, tentative arrival and injection times, subject initials (if known), and a reminder about the cancellation policy.
- If you cannot use the slot, we ask that you notify us by email no later than ten (**10) calendar days** in advance of the scheduled scan. There will be no charge for slots cancelled by this deadline.
- **Cancellations occurring nine (9) calendar days to four (4) business days** prior to a scheduled scan date will be assessed a **fee*, provided cancellation notice is received by 3pm, four (4) business days** prior to a scheduled slot).
- Seven (7) calendar days before a scheduled slot, you will receive a second email reminder that will include confirmation of arrival and injection times and a request for subject identifying information and the signed consent (if not already received).
- By 3PM, three (3) business days before a slot, we must receive subject identifying information. If no information is sent, the slot may be cancelled.
- There will be a **fee* for scans cancelled later than 3pm, four (4) business days** in advance of a scheduled slot.
- Cancellation charges may be waived under certain circumstances including: 1) acute medical problems with the subject, 2) failure to place an arterial line that is necessary for the study.
- *Cancellation fees are listed in the Yale University PET Center Services Price List

Please refer questions on scheduling to PET.scheduling@yale.edu

Consent Documentation Required for Human PET Studies

The following signed subject consent documentation and laboratory/EKG results (if applicable) must be submitted to the Yale University PET Center a minimum of 3 business days **prior** to a scheduled PET scan date:

1) Copy of the last page of a VALID CONSENT FORM signed and dated by the research subject and person obtaining consent. To be considered valid, the date of the signatures must be between the approval and expiration dates as listed on the document. The consent must include:
   - **HIC protocol #, study cohort (i.e., Healthy Controls; Experimental Groups), date, and version # clearly identified in the header and footer of the consent form;**
   - **HIC approval stamp and box with expiration date and HIC signature, or HIC COEUS approval/expiration dates.**
2) Copy of the current HIC/IRB approval letter. To be considered valid, the planned scan date must be before the expiration date listed on the letter.
3) Copy of the current YNHH Radiation Safety Committee (YNHHRSC) approval letter or Yale University RDRC (YURDRC) approval letter. To be considered valid, the planned scan date must be before the expiration date listed on the letter.
4) Copy of subject's screening laboratories and EKG results for all studies using an arterial line or pharmacologic compound (cold non-radioactive drug).

Before any actions take place by Yale University PET Center staff, these documents will be checked for completeness and validity.

IMPORTANT NOTES

- If procedural changes (e.g., new blood draws, new EKG) are made, or new risks are added to the protocol/consent since the signature date on the consent, the subject must sign a new amended/HIC-approved consent and a new HIC approval letter must also be submitted to the PET Center.
- If the protocol was amended to increase subject numbers, amendment approval letters from the YNHHRSC or YURDRC, and HIC must be submitted to the PET Center.

IMPORTANT: The Principal Investigator is responsible for ensuring that the correct version of the consent has been signed by the subject within a valid time frame.

Please refer questions on consent documentation to Shannan Henry (shannan.henry@yale.edu)

PET Human Protocol Review Process

Initial consultation:

To facilitate the protocol review process, it is strongly recommended that you consult with the PET Center faculty and staff PRIOR to submitting your protocol to the IRB. Please see our web site for faculty contacts: (http://petcenter.yale.edu/research/collaborative.aspx)

Yale University PET Center
801 Howard Avenue
PO Box 208048
New Haven, CT 06520-8048
Ph: (203) 737-YPET
Fax: (203) 785-3107
General email: pet.center@yale.edu
Website: http://petcenter.yale.edu/

PET Protocol Review Process – Yale HIC

1. PI sends draft of protocol/consent(s)/etc. to PET Center faculty member to initiate review/comments from appropriate PET Center investigators/staff PRIOR to submission to HIC/other committees.

2. PET Center designates a lead PET Investigator to coordinate protocol review process with PI and assigns an abbreviated code name (aka "short name") for the protocol to be used in communications. PET investigators/staff review protocol and informed consent documents (ICD) and provide PI with a spreadsheet containing all required/recommended PET comments/edits to incorporate into the protocol documents. This review takes approximately ten business days and focuses on issues such as: inclusion of PET study personnel, confirmation of accuracy of radiation dosimetry, confirmation of accuracy of defined PET procedures. PET reviewer comments are defined as Required Changes (R); Suggestions (S); Questions (Q); Comments (C).

3. All studies are evaluated by the Medical Director and PET Protocol Review Committee to assess the medical level of supervision required (e.g., whether a MD must be present for the scan) based on the level of risk (e.g., whether a study involves pharmacologic compounds with known serious side effects or a subject group requires special care).

4. PI reviews spreadsheet and responds to each entry in the PI Reviewer Columns, indicates if the change was made, adds any comments/answers to questions, and includes initials. PI edits protocol and consent documents accordingly and re-submits completed spreadsheet documents to lead PET Investigator or their designee. NOTE: All *Required* changes must be made in order to receive PET approval via Coeus.

5. If the protocol involves the Magnetic Resonance Research Center (MRRC), PI completes the Proposal for Use of MRRC Resources form found on the MRRC website (http://medicine.yale.edu/mrrc).

6. PI submits the protocol/consent(s), MRRC documentation, and any other required documents to HIC via COEUS website (https://coeusirb.its.yale.edu/coeus). Please refer to the COEUS training website (http://www.yale.edu/coeus/training.html) to access quick guides for specific functions, as well as a detailed COEUS training manual. If you need further assistance, please contact the HIC directly at http://www.yale.edu/hrpp. PI's are also advised to consult HRPP website to ensure that the most recent protocol and consent template are used.

IMPORTANT: Be sure to list the Yale University PET Center as a performing **Organization** to ensure that the protocol is correctly routed to the PET Center for approval. Failure to do so will delay protocol approval.

7. HIC COEUS review process:

A. HIC reviewer does an initial review/triage of all documents and may request additional info/corrections from the PI. HIC reviewer then approves the documents for routing to MRRC/PET/YCCI* reviewers.

B. PET/MRRC/YCCI* committees review documents and may request additional info/corrections from the PI. If the PET Center has reviewed the protocol in advance (see above), the PET review will occur quickly. The protocol will be approved if all *Required* changes from the spreadsheet were made. If the PET Center has not reviewed the protocol in advance, this review will take a minimum of 10 business days. Once all approvals have been obtained, the documents are routed for full HIC review.

*Note: Phase 1 protocols utilizing YCCI services, such as the Hospital Research Unit (HRU) inpatient and outpatient facility, or the Church Street Research Unit (CSRU) outpatient facility, are subject to review by the YCCI Science and Safety Committee. This committee currently meets 1 time per month to review/approve protocols. All other protocols will be reviewed for resource utilization and feasibility only by the Office of Research Services. The reviews are conducted on a rolling basis and can take up to 5-7 business days.

C. HIC committee members review and set a committee meeting date. HIC committee may request revisions. If so, the PI must provide annotated responses to the HIC revision requests; HIC committee approves.

PET Protocol Review Process – Non-Yale IRB

Yale/Pfizer protocols involve review/approval through an outside IRB (WIRB) and utilize different forms/templates. Contact Amy Turner at the Yale University PET Center (amy.turner@yale.edu) for assistance.

PET Protocol Review Process – Amendments that Increase Radiation

Protocol Amendments that increase radiation exposure to human subjects must be reviewed and approved by the Yale University PET Center, and either the Yale-New Haven Hospital Radiation Safety Committee (YNHHRSC) for IND radiotracers, or the Yale University Radioactive Drug Research Committee (YURDRC) for radiotracers under RDRC purview. Prior to initiating an amendment affecting radiation, please send an email description of the amendment to Amy Turner (amy.turner@yale.edu). Indicate the purpose and new aim(s) for the amendment and indicate the source of the radiation increase:

- increase in number of subjects in current study cohort(s)
- addition of a new aim with a new study cohort
- increase in number of current radiotracer injections/scans
- addition of a new PET radiotracer

The PET Center will assist in determining if an amendment is appropriate, or may recommend that drafting a new protocol is a better option. Once the amendment/new protocol is drafted, it should be sent to amy.turner@yale.edu for PET Center review.

Note that protocol amendments involving increased radiation exposure will also need to be submitted to either the YNHHRSC or YURDRC for review and approval. Contact Shannan Henry (shannan.henry@yale.edu) for assistance in drafting the YNHHRSC or YURDRC amendment submissions. It is recommended that submission of the amendment to YNHHRSC or YURDRC be done concurrent to submission to the HIC. This will enable timely reviews and approvals by both committees. Note that YNHHRSC or YURDRC amendment review and approval takes approximately 1 month.

PET Protocol Review Process – Renewals

HIC reapproval:
It is important to submit your protocol renewals to the HIC as soon as possible in order to avoid interruption in your PET scanning schedule. The HIC reapproval process can take approximately 2 months to complete. Please refer to the HRPP website for the HIC renewal form and instructions. http://www.yale.edu/hrpp/

YNHHRSC reapproval (required for protocols using IND radiotracers only):
In addition to HIC reapproval, protocols using IND radiotracers will also need to be reapproved by the YNHHRSC. This renewal process takes approximately one week.

As soon as you receive HIC reapproval, please submit the HIC reapproval letter and reapproved protocol and consent documents to Shannan Henry (shannan.henry@yale.edu) and cc Amy Turner (amy.tuner@yale.edu). Shannan will then submit the YNHHRSC renewal application to Dr. Ravinder Nath.

If you work directly with the YNHHRSC for your protocol reviews/approvals, as soon as you

receive HIC reapproval, please submit the YNHHRSC renewal application to Dr. Ravinder Nath, along with the HIC reapproval letter/ protocol/ consent documents. Please refer to the YNHHRSC website for the renewal application and instructions: http://rsc.med.yale.edu/login.asp?url=myApps.asp

IMPORTANT: To ensure that scanning schedules are not interrupted, the PET Center must receive the HIC reapproval letter, reapproved protocol/consents, and the YNHHRSC reapproval letter prior to the protocol expiration date. If the protocol has expired and complete reapproval documentation has not been received, scans will need to be cancelled or rescheduled.

Please refer questions on the human protocol review process to Amy Turner (amy.turner@yale.edu)

Radiation Safety Review Process

Three radiation safety committees, the Yale-New Haven Hospital Radiation Safety Committee (YNHHRSC),the Yale University Radioactive Drug Research Committee (YURDRC), and the Yale University Radiation Safety Committee (YURSC) review human PET protocols.

All PET protocols must be reviewed by ***either*** the **Yale-New Haven Hospital Radiation Safety Committee (YNHHRSC)** ***or*** the **Yale University Radioactive Drug Research Committee (YURDRC)**. These committees are responsible for review of protocols involving research use of radiopharmaceuticals in human beings:

The YHNNRSC reviews protocols with IND radiotracers.
The YURDRC reviews protocols with radiotracers under RDRC purview.

All PET protocols must also be reviewed by the **Yale University Radiation Safety Committee (YURSC**). This committee is responsible for safety of radiation workers.

This review process occurs **concurrently** with the HIC review. To ensure smooth approvals, PET Center staff coordinates this process. The PI ensures that the lead PET Investigator and PET RSC/RDRC Coordinators (Shannan Henry/Amy Turner) have electronic copies of the protocol and Informed Consent Document (ICD) versions that will be submitted to the HIC, along with the correct HIC number obtained from COEUS. This team then works together to complete either the YNHHRSC web application or the YURDRC application and submit the protocol documentation to the appropriate Radiation Safety Committees (either YNHHRSC ***or*** YURDRC), as well as YURSC (all protocols)

Each protocol has a Principal Investigator. However, for the purposes of radiation reviews and for protocols in which the only radiation dose to the subjects is from PET, submission of forms will be the responsibility of a lead PET Investigator in the PET Center in consultation with the PET RSC/RDRC coordinators. (*NOTE: If a PI submits an application/protocol directly to the YNHHRSC or YURDRC without PET Center assistance, he or she must notify the lead PET Investigator and PET RSC/RDRC Coordinators (Shannan Henry/Amy Turner) and send them a copy of the submitted YNHRSC or YURDRC application and protocol documentation.)*

Important:

A) Dosimetry entered into YNHHRSC or YURDRC must match the dosimetry included in the protocol and consent form(s). Note that detailed dosimetry chart information is generally not required in the HIC protocol.

B) YNHHRSC web application is on http:/rsc.med.yale.edu.

C) YURDRC application and submission instructions are on HRRP website: http://www.yale.edu/hrpp/forms-templates/index.html

D) Once obtained, the YNHHRSC or YURDRC approval is submitted to COEUS as a “Notify IRB” step. This is necessary for the HIC to release the approved ICD.

E) Once all required Radiation Safety approvals & HIC approval letter are obtained, the Authorized User (AU) form is completed by RSC/RDRC Coordinator and Chief PET technologist. This form is the authorization to administer radiopharmaceuticals to humans under the NRC license. The AU form and approved protocol/consents are then sent via email to an Authorized PET User for signature.

Radioactive Drug Research Committee (RDRC):

Administration of radiopharmaceuticals to humans can be performed under the auspices of either an IND from the FDA, or under the auspices of the Yale University Radioactive Drug Research Committee (YURDRC). The IND/FDA route is used for radiopharmaceuticals that have never been administered to human beings before. The YURDRC route is used for radiopharmaceuticals that have been used in human studies and are designed for basic science research. Thus, most PET tracers at the PET Center are approved via the YURDRC route.

YURDRC approval requires submission of drug manufacturing and quality control procedures. Radiochemistry faculty and staff perform the submission to the YURDRC at the time of the first use of a tracer.

Protocols that use tracers approved by the YURDRC have a few additional reporting steps, as follows:

RDRC Annual Reports

The PET RSC/RDRC Coordinator assists in the completion of the FDA Form 2915 for Annual RDRC Reports. These forms are due to the FDA at the end of January. The PET RSC/RDRC Coordinator will produce these forms including compilation of yearly radiotracer dosimetry for each subject studied on every protocol reviewed by the YURDRC. The PI or lead PET Investigator must sign these forms and submit the form directly to the YURDRC Chairperson (cc: shannan.henry@yale.edu, amy.turner@yale.edu).

RDRC FDA Form 2915 Special Summary Reports

When a protocol to be reviewed by the YURDRC will involve more than a total of 30 subjects, an FDA Form 2915 Special Summary report must be completed and submitted along with the protocol/consent(s) to the YURDRC Chairperson. The RSC/RDRC Coordinator will initiate the form, complete as much as possible, and forward to the appropriate PI/ lead PET Investigator for review. The lead PET Investigator or PET RSC/RDRC Coordinator will submit the form directly to the YURDRC Chairperson.

Please refer questions on radiation safety review to Shannan Henry (shannan.henry@yale.edu)

Standard Protocol Language

This section provides suggestions for standard language for use in HIC protocols. This language has been previously approved by the HIC, so use of this language will likely facilitate protocol review and approval. For assistance in drafting PET protocols, please contact Amy Turner (amy.turner@yale.edu).

Important: It is the PIs responsibility to ensure that PET standard language is current at the time of protocol renewal.

Required Protocol Information

Performing Organizations
Check Yale University PET Center as study site

Additional Required Documents
Check YNHH-Radiation Safety Committee (YNHH-RSC) approval or Yale University Radioactive Drug Research Committee (RDRC) approval

Research Team
Ming-Kai Chen, (or another NRC-approved authorized user for medical use) must be listed as Authorized PET User
David Matuskey (or other YNHH credentialed MD) must be listed as PET study physicians
For PI's outside of Yale, Yale consenting personnel should be included

Exclusion Criteria
Subjects with history of prior radiation exposure for research purposes within the past year such that participation in this study would place them over FDA limits for annual radiation exposure. This guideline is an effective dose of 5 rem received per year.

Subjects with current, past or anticipated exposure to radiation in the work place within one year of proposed research PET scans.

For Protocols with Arterial Lines:
Blood donation within eight weeks of the start of the study.

History of a bleeding disorder or are currently taking anticoagulants (such as Coumadin, Heparin, Pradaxa, Xarelto).

For Protocols that will allow MRI Data Sharing:
If an MR image is already on file at the PET Center, and has been collected within a reasonable time period, a new MRI may not be collected.

Protocol: Risks

Risks Associated with Unknowns
The subject's health and safety will always be the primary concern of the doctors and staff performing the study. In the event of an unexpected outcome, all necessary medical action will be taken.

Medication might be administered as needed, per the Yale PET Center standard operating procedure for medical emergencies, in order to treat complications.

Risks Associated with Radiation (for studies using a single radiotracer):
The Yale-New Haven Hospital Radiation Safety Committee (YNHHRSC) (or Yale University Radioactive Drug Research Committee (YURDRC) - *list appropriate committee)* will review the use of radiation in this research study, and no subjects will be scanned until RSC **(or RDRC)** approval is obtained. This research study involves exposure to radiation from **(insert radiotracer name)** PET scanning. This radiation exposure is not necessary for medical care and is for research purposes only.

The targeted amount of radiation an individual subject will receive in this study is from **(insert #)** injection(s) of ≤ **(insert dose)** mCi of **(insert radiotracer name),** plus transmission scans *(if using mCT scanner add: "and/or CT scans")***.**

Optional Text (to allow for additional injection should PET scan fail):
*However, in situations where a PET scan is not successful following a **(insert radiotracer name)** injection (e.g., problems with the PET camera), the subject may receive an additional (**insert radiotracer name)** injection, up to a total of **(insert #)** injections of **(insert radiotracer name)** during the study, if deemed appropriate.*

Although each organ will receive a different dose, the maximum amount of radiation exposure subjects will receive from this study is equal to an effective dose equivalent of **(insert #)** rem for a total of up to **(insert total dose)** mCi of **(insert radiotracer name)** in **(insert #)** injection(s). (**insert #** injection(s) is(are) required under normal conditions). This calculated value is used to relate the dose received by each organ to a single value.

The amount of radiation subjects will receive in this study is below the dose guidelines established by the FDA and monitored by **the Yale-New Haven Hospital Radiation Safety Committee (or Yale University Radioactive Drug Research Committee - *list appropriate committee*)** for research subjects. This guideline sets an effective dose limit of 5 rem per year.

Risks Associated with Radiation (for studies using multiple radiotracers):
The Yale-New Haven Hospital Radiation Safety Committee (YNHHRSC) (or Yale University Radioactive Drug Research Committee (YURDRC) - *list appropriate committee)* will review the use of radiation in this research study, and no subjects will be scanned until RSC **(or RDRC*)*** approval is obtained. This research study involves exposure to

radiation from **(insert radiotracer name)** and **(insert radiotracer name)** PET scanning. This radiation exposure is not necessary for medical care and is for research purposes only.

The targeted amount of radiation an individual subject will receive in this study per year is from **(insert #)** injection(s) of ≤ **(insert dose)** mCi from **(insert radiotracer name)** and from **(insert #)** injection(s) of ≤ **(insert dose)** mCi from **(insert radiotracer name)**, plus transmission scans *(if using mCT scanner add: "**and/or CT scans**")***.**

Optional Text (to allow for additional injection(s) should PET scan fail):
*However, in situations where one or both PET scans are not successful following injection (e.g., problems with the PET camera) the subject may receive an additional **(insert radiotracer name)** and/or **(insert radiotracer name)** injection, up to a total of **(insert #)** injections of **(insert radiotracer name)** and **(insert #)** injections of **(insert radiotracer name)** during the study, if deemed appropriate.*

Although each organ will receive a different dose, the maximum amount of radiation exposure subjects will receive per year from this study is equal to an effective dose equivalent of **(insert #)** rem for a total of up to (**insert #)** injection(s) of (**insert dose**) mCi of **(insert radiotracer name)** and up to (**insert #)** injection(s) of (**insert dose**) mCi of **(insert radiotracer name).**

Optional Text for effective dose equivalent including additional injection(s):
*In the event that the subject receives an additional **(insert radiotracer name)** and **(insert radiotracer name)** injection, the subject will receive an effective dose equivalent of **(insert #)** rem for a total of up to **(insert total dose)** mCi of **(insert radiotracer name)** in **(insert #)** injections and up to **(insert total dose)** mCi of (**insert radiotracer name)** in **(insert #)** injections.*

That is, a total of **(insert #)** rem for **(insert #)** scans is the maximum amount of radiation exposure that a subject will receive per year from the study. This calculated value is used to relate the dose received by each organ to a single value.

Optional Text (effective dose equivalent with additional injection(s for entire study):
*Over the **(insert total # of months/years)** duration of this study, subjects will receive an effective dose equivalent of (**insert #)** rem from a total of **(insert #)** injections of (**insert single dose**) mCi of (**insert radiotracer name)** and **(insert #)** injection(s) of (**insert single dose**) mCi of (**insert radiotracer name)**. In the event that the subject receives additional (**insert radiotracer name)** and (**insert radiotracer name)** injections, the subject will receive an effective dose of (**insert #)** rem for a total of **(insert total dose)** mCi of (**insert radiotracer name)** in (**insert #)** injections and **(insert total dose)** mCi of (**insert radiotracer name)** in **(insert #)** injections. That is, a total of up to (**insert total #)** rem for (**insert total #)** scans is the maximum amount of radiation exposure that a subject will receive from completing the entire study.*

The amount of radiation subjects will receive in this study is below the dose guidelines established by the FDA and monitored by **the Yale-New Haven Hospital Radiation Safety**

Committee (or Yale University Radioactive Drug Research Committee *- list appropriate committee)* for research subjects. This guideline sets an effective dose limit of 5 rem per year.

Risks Associated with Blood Drawing and IV line Insertion:
Drawing blood and inserting an intravenous line (IV) into an arm vein are safe and standard medical procedures. Sometimes a bruise will occur at the puncture site and rarely, a blood clot or infection will occur in the vein. Certain individuals may feel light-headed during venipuncture. The volume of blood collected during this study, including screening laboratories, will be approximately **(insert #)** tablespoons. This is not expected to have any serious negative effects on a study participant.

(Note: PET scans of 2-hour duration with arterial lines require approximately 6 tablespoons (90 mL) of blood per scan in addition to any blood draws needed for screening labs/ tests. For PET scans with arterial lines that have a duration of greater than 2 hours, please increase this blood draw amount by an additional 3 tablespoons (45 mL) per scan for a total of up to 135 mL per scan).

Risks Associated with Use of an Arterial Catheter:
On the PET scan day, a radial arterial catheter will be inserted. Certain individuals may feel light-headed during arterial catheter placement. Arterial catheter placement may be associated with mild-to-moderate pain, hematoma, inflammation, bleeding, or bruising at the puncture site. If any of these, or other, symptoms occur and do not diminish within 24 to 72 hours after the arterial line removal, or in the event that they worsen, subjects should be advised to call the on-call doctor listed on the PET discharge instructions. In rare instances blocking of the artery, tearing of the artery, arterial leakage, poor healing, or infection at the catheter insertion site may occur.

Note: The PET Center does **not** use the Allen's Test to assess arterial blood flow prior to arterial line insertion, as this test is not reliable (only 54% success rate) as cited in published literature (Jarvis, MA, Jarvis CL, Jones PRM, Spyt TJ, Reliability of Allen's Test in Selection of Patients for Radial Artery Harvest, *Ann Thor Surg,* 70:1362-1365, 2000;).

Protocol: Minimizing Risks

Risks Associated with Radiation:
The dose of radiation will be submitted for approval to **the Yale-New Haven Hospital Radiation Safety Committee (YNHH RSC) (or Yale University Radioactive Drug Research Committee (YURDRC) *- list appropriate committee)***. All scans will be done in the presence of medical supervision and trained staff in an institution specifically designed to support imaging studies. In the event of serious medical complications, the PET scan facilities have immediate access to or consultation with specialized medical units at the Yale-New Haven Hospital**.** Preparation of radiopharmaceuticals and performance of PET scans

will be by radiochemists, physicians, and technologists of the Department of Diagnostic Radiology, Yale University School of Medicine. These professionals are qualified by training and experience in the safe use and handling of radiopharmaceuticals. Subjects will be asked about their previous radiation exposure and those who have had research exposure within the past year will be excluded if their cumulative annual exposure (including the present study) exceeds FDA limits. The information on the previous radiation exposure of study subjects will be notified to the study doctor.

If women are included:
No PET studies will be performed on pregnant or potentially pregnant women, as confirmed by pregnancy testing during evaluation and on each scan day before initiation of any scan procedures. If subjects are breastfeeding they will not be able to participate in this research study.

Risks Associated with Blood Drawing & IV Line Insertion:
The risks of bruising, clotting, and infection will be minimized by having venipuncture performed by trained and experienced personnel using aseptic technique. To avoid injury due to fainting, the catheter will be inserted when the subjects are in a recumbent position. The blood draws during PET scanning sessions will be obtained from the already inserted catheter, to minimize discomfort.

For studies with arterial lines:
Risks Associated with Use of an Arterial Catheter:
Risks of radial artery cannulation are minimized by having the procedure performed by an experienced physician. Pain is minimized by local anesthesia. Infection is avoided by adequate cleansing of the skin prior to intravascular line insertion. After arterial catheter removal, bleeding is prevented by direct pressure applied to the site for a minimum of 15 minutes followed by a pressure dressing (coban) that should be kept clean and dry until evening. Subjects will have their hand and finger blood supply examined after arterial cannulation throughout the study, and again following catheter removal. Also, subjects will be asked to abstain from aspirin and other NSAIDs for 7-10 days prior to arterial line insertion and 7-10 days following arterial line removal. Subjects will be provided a 24 hour emergency physician contact number to call if they encounter pain, discoloration, numbness, tingling, coolness, hematoma, inflammation, or any other unusual symptoms in the wrist or hand, or fever, chills or drainage from the vascular puncture sites, following the procedure. In addition, if an emergency arises at the time of cannulation or scanning, 911 will be called, and the subject will be sent to the Emergency Department for evaluation and treatment. A nurse will provide discharge instructions outlining general instructions in addition to post-arterial catheter precautions, problems to watch for, and procedures to follow should such problems occur.

Required Consent Information

PET Scanning Procedure with Arterial Catheter Insertion:
An experienced physician will insert an arterial catheter in your wrist area. The arterial catheter is about 2 inches long and looks like a regular IV tube, but it is inserted into an artery, not a vein. The blood flow in the arteries can tell us about your blood pressure. If an arterial catheter is in place, we can measure your blood pressure continuously. The other main reason to put in an arterial catheter is to be able to draw blood samples rapidly, repeatedly, and without causing you pain. Here is what happens when an arterial line is placed. First, the skin is cleaned with betadine solution (contains iodine).. This skin cleansing with an antiseptic aims to reduce the microorganisms present on the skin and therefore reduce the risk of an infection. Second, the insertion area is numbed with a local anesthetic, so that you feel less pain when the catheter is inserted. You will probably just feel pressure but may also feel pain. This pain is usually like the pain you feel when an IV is placed and only rarely is it worse. Third, the catheter will be flushed regularly during your scan with saline (a salt solution), which prevents clogging of the catheter with a blood clot. Fourth, after the catheter is removed, local pressure is applied for a minimum of 15 minutes to prevent bleeding under the skin. A pressure dressing (coban) and clear dressing (tegaderm) will then be applied and you will be asked to keep it clean and dry, avoid strenuous exercise, refrain from lifting heavy objects weighing more than 5 pounds, and to avoid repetitive movements for 48 hours. You may remove the pressure dressing at bedtime and the clear dressing after 48 hours, but do not submerge your hand and wrist in water for a full 72 hours. Since the catheter is in for a minimal period, there is a low risk of infection.

Risks Associated with Blood Drawing & IV Line Insertion:
Drawing blood and inserting an intravenous line (IV) into an arm vein are safe and standard medical procedures. Sometimes a bruise will occur at the puncture site and rarely a blood clot or infection will occur in the vein. You should not donate blood for at least eight weeks after the study. The total volume of blood collected during this study will be up to **(insert #)** tablespoons, including blood drawn from your vein for the screening laboratories and blood drawn from your vein and/or artery during the **(insert #)** PET scan day(s). This amount of blood loss is safe for study participants.

Risks Associated with Use of an Arterial Catheter

Important: If you have a history of a bleeding disorder or are taking medication to thin your blood, you will not be allowed to participate in this study.

Putting in the plastic tube into the artery in the wrist area may cause bruising, and potentially infection. The arterial puncture may also cause spasm or clotting of the artery with a temporary decrease in blood flow, hematoma (swelling of blood within the tissues), bleeding, or inflammation. If this occurs, signs and symptoms will dissipate over time, usually 24 to 72 hours after the event. In rare instances, blocking of the artery, poor healing, or infection at the catheter insertion site may occur. Insertion of arterial catheters for sampling blood may be associated with mild-to-moderate pain or bruising at the puncture site. To minimize these

risks, an experienced physician will insert the arterial line and a trained nurse will oversee subject care.

For two days following the placement of the arterial line, you should check your wrist/arm daily. If you experience any excessive pain, tenderness, swelling, redness, drainage, skin color changes, numbness, pins and needles, or decreased strength in the arm that had the catheter, you should immediately call your study team or the PET Center Physicians Dr. David Matuskey at 203-370-1403 (pg) or Dr. Ming-Kai Chen 203-766-4241 (pg) (You will need to punch in your tel. number with area code followed by the, "#," sign).

You may experience a rare allergic reaction to the medicine used to numb your skin prior to placement of the arterial catheter. If you have had a bad reaction to lidocaine, novocain, or other anesthetic agents used to numb the skin in the past, please tell us about this experience before you go through the arterial line placement. Severe allergic reactions can be life threatening. You will also be asked to abstain from using aspirin and other anti-inflammatory drugs (such as Motrin or Aleve) for 7-10 days before arterial line placement and 7-10 days after arterial line removal.

Risks Associated with Radiation
This research study involves exposure to radiation from positron emission tomography (PET). Please note that this radiation exposure is **not** necessary for your medical care and is for research purposes only.

The targeted amount of radiation you will receive during the **(insert #)** PET scan sessions in this study is from **(insert #)** injection(s) of **(insert radiotracer(s))** and from transmission scans *(if using mCT scanner add: "and/or CT scans")* used to help obtain the PET images.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from this study is equal to a uniform whole-body exposure of **(insert #)** rem, which is the equivalent of approximately **(insert #)** years of natural environmental exposure. This value is known as the "effective dose equivalent" and is used to relate the dose received by each organ to a single value. This amount of radiation exposure is below the annual limit of 5 rem set by the federal government for research subjects.

The effects of radiation exposure on humans have been studied for over 60 years**.** In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful and may cause cancer at any dose- even low doses such as those received during this research.

Please tell your study doctor or other study personnel if you have taken part in other research studies at Yale or other places/hospitals that used radiation. This way we can make sure that

you will not receive too much radiation. You should consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body. Before you take part in any future studies that use radiation, you should also tell those study doctors about your participation in this study.

If you are pregnant or breast feeding, you may not participate in this research study. It is best to avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults. We will perform urine pregnancy tests prior to your participation on your PET scan day(s).

For studies that will allow MRI Data Sharing:
If you have an MR image already on file at the PET Center, and it has been collected within a reasonable time period, a new MRI may not be collected.

Suggested Protocol & Consent Information

Study Procedures

Re-Screening

> ***Suggested Consent Text:***
> In the event that your PET scanning session is postponed and is scheduled to occur more than 3 months after your screening visit, you may be asked to return for an additional screening visit. This is to ensure that you still meet all of the study criteria. This visit may include additional blood work and a physical exam. You will be compensated $XX, depending on the procedures completed.

Cancellations

> ***Suggested Consent Text:***
> In the event that your PET scan day gets cancelled for reasons outside of your control (such as radiotracer synthesis failure), you will receive a minimum payment of $XX per cancelled scan, or a higher amount not to exceed the amount for a full scan day. This amount will be based on your length of participation on the scan day prior to cancellation, and will be up to the discretion of the PI.

Replacement Subjects
If you plan to replace withdrawn subjects with newly enrolled subjects, you must state this in the protocol and indicate the number of subjects (per study cohort) that may be added.

> ***Suggested Protocol Text:***
> In the event of subject withdrawal prior to completing all PET scans or that the collected data is corrupted despite the scan being completed, a new subject will be enrolled and scanned. Up to **(insert #)** subjects **(specify each subject cohort, i.e.,**

healthy, experimental) may be injected with **(insert radiotracer name)** in order to complete **(insert #)** subjects.

Economic Considerations/Compensation

Arterial Line Placement Compensation
For studies with arterial lines, we recommend that the PET scanning payments be divided into 2 components: arterial line placement & scanning (example: $XX for arterial line placement and $XXX for completion of PET scan). This should be stated in both the protocol and the consent.

Transportation Compensation
PET Center recommends that reasonable transportation costs be reimbursed to subjects whenever possible.

Suggested Protocol Text:
Reasonable transportation costs will be reimbursed. Receipts must be submitted. Subjects will be required to contact the study coordinator prior to their study date to discuss transportation plans and confirm that they will be appropriate for reimbursement.

Suggested Consent Text:
Reasonable transportation costs will be reimbursed. Receipts must be submitted. Please contact the study coordinator prior to your study date to discuss your transportation plans and confirm that they will be appropriate for reimbursement.

Direct Payment of Transportation Costs
In special circumstances, direct payment of transportation costs may be possible:

Suggested Protocol Text:
In certain instances, it may be possible for the subjects' transportation costs to be paid directly by the PET Center/ Principal Investigator. This must be approved and arranged through the study coordinator prior to the subjects' study dates.

Suggested Consent Text:
In certain instances, it may be possible for your transportation costs to be paid directly by the PET Center/ Principal Investigator. This must be approved and arranged through the study coordinator prior to your study date.

Compensation for Back-up Subjects
PET Center recommends that subjects be asked if they would be willing to placed on "back-up" status, i.e., subjects who may be called to come to replace another subject who has cancelled a scan. "Back-up" subjects would agree to be available on a specific scan date/time. "Back-up" subjects would be compensated for their time and would receive payment whether or not they participate in an actual scan.

Suggested Protocol Text: Back-Up Subjects
A back-up subject may be scheduled on the PET scan day in order to prevent study cancellation if a participant does not keep their appointment. Back-up subjects will be individuals that have met screening requirements and are available to scan in the event of primary participant cancellation.

Suggested Consent Text: Acting as a Back-Up Subject
You may be asked to act as a back-up subject. This means you have already been screened to participate in the study, but have not yet been scheduled for a study session. It would mean being "on-call" in the event of a last minute cancellation. You would arrive at the PET Center and stay on site until the scheduled participant has begun the study. You would be paid for your time. If the scheduled participant cancels or is unable to continue, you would then complete the study that day(s), and be paid for the study procedures as listed in this consent form.

Permission to Contact Subjects for Future Studies:

Suggested Consent Text: Possible Participation in Future Studies
We would like to be able to contact you in the future to offer you participation in other studies. Giving your permission for the research team to contact you does not obligate you to answer any future questions or to participate in any future research – you always have the right to decline further participation in research. If you agree to participate in another study, we would ask you to read and sign a new consent form. Please initial if you would like to be contacted to participate in other studies.
I agree to be contacted for future research studies: _____.
Participant's Initials

Please refer questions on protocol and consent language to Amy Turner (amy.turner@yale.edu)

Yale University PET Center Data Repository

Purpose

The purpose of the Yale University PET Center Data Repository is to collect and archive relevant healthy control PET data to be shared (with permission) across past, current and future research projects involving PET imaging of the brain and body. The PET repository enables data sharing between investigators from multiple studies and benefits research by minimizing individual subject radiation exposure rates while maximizing the benefits of our scientific research. The ability to share data between protocols assists in generating new grant applications for studies, fostering collaborations, facilitating publications, and expanding scientific knowledge of PET research.

Background

PET research has advanced medicine and science by allowing researchers to study *in-vivo* molecular changes across various states of health and disease. PET scans are well tolerated with minimal medical risk to the subjects, nevertheless, research could be furthered by lessening burden to research subjects (e.g., radiation exposure and arterial line placements) and increasing the statistical power to investigate medical and scientific questions. This repository allows us to lower overall research subject burden, more efficiently use subject data and improve technical methods to ensure the reliability of PET data.

Specifically, the PET Data Repository enables researchers to share technical and clinical data including:

Technical Imaging Data
Radiotracer name
Radiotracer input function and metabolite data
PET raw data
DICOM image files from PET and PET/CT and MR systems
Parametric images derived from DICOM images
Calculated regional values
Radiotracer administration information
Arterial Line Blood Data
Motion correction data

Clinical PET Data
Neuropsychiatric measures
Demographics (age, gender, race, height, weight, education level)
Date and time of scan
Lab test results

With the goal to enable researchers to:

Re-analyze, re-process and “fine-tune” PET data
Create new grant submissions
Write new PET publications / enhance publications in process
Increase subject size of healthy controls to strengthen proposals and protocols

Board of Governors

The PET Center Repository Board of Governors (BOG) has overall approval authority for PET data requests. Each member of the BOG has the authority for final sign off/approval to release data to requesting investigators. The board meets on an annual basis (and as needed) to review data processes, resolve any potential issues, and make improvements. Members of the BOG include David Matuskey, MD (PET Center Data Repository PI); Richard Carson, PhD (Co-Investigator); Ming-Kai Chen, MD, PhD (Co-Investigator); Shannan Henry (Clinical Research Associate); and Amy Turner (PET Center Data Repository Manager).

The PET Center Data Repository Process

Data that has been collected by investigators conducting research at the Yale PET Center will be coded and distributed for secondary research purposes only after the requesting investigator has completed and submitted a Yale University PET Center Data Repository Request Form (see form on **pg. 37** of this guide). The requesting investigator must state the intended research purpose on this form and indicate what type of PET Data is requested.

The requesting investigator will submit the form to the PET Center Data Repository Manager **(amy.turner@yale.edu)** who will review the request and identify which HIC protocols contain the requested healthy control data. The Data Manager will then submit the request form to the PET Data Repository PI for initial review/email approval to proceed, contact the PI (owner) of the requested data to obtain PI approval (for each individual protocol) via email correspondence, and coordinate with the appropriate PET Center staff to execute the data request. Prior to distribution, a member of the BOG will approve the Repository Request form.

Data distributed to researchers participating in the PET Center Repository will be extracted from the password-protected internal PET Center Network server data and issued to the investigator in a coded manner, i.e., subject identifiers such as name, birth date and other ePHI will be stripped from the data prior to release. However, time and date of scan will be provided to investigators, as this information directly impacts the utility of the data for further research and analysis. Specifically, due to the short half lives of PET tracers, data and image processing must account for exact scan times, e.g., in radioactive decay calculations. The

PET Data Manager will track and retain distribution records of PET Repository Data to recipient investigators.

Subject Consent Process

Healthy adult research subjects (age >18) who have consented to participate in PET scan imaging at the Yale University PET Center will be invited to donate their data into the registry. Each of these subjects will have been previously recruited for PET studies conducted by Yale PIs under guidelines of the Yale University Human Investigation Committee (Yale HIC).

The Yale University Human Investigation Committee (HIC) has granted a waiver of informed consent and a waiver of HIPAA authorization for all healthy control subjects scanned prior to 12/12/2014. However, going forward, consent must be obtained from all healthy control subjects to allow their data to be included in the repository. Healthy control subjects enrolled in active PET protocols will be consented for participation by PET Center personnel at the time of their next scheduled PET scan visit. They will be asked to sign a separate consent form specifically related to the PET Center Data Repository.

Please refer questions on the PET Center repository process to Amy Turner, PET Center Data Repository Manager (amy.turner@yale.edu) or David Matuskey, MD, PET Data Repository PI (david.matuskey@yale.edu).

Information for Grant Applications

Budget Justification for PET Scan Costs

The Yale PET Center is an internal service provider and rates are set following the NIH guidelines.

For studies with radiosynthesis and PET scans: The full PET study cost includes chemistry personnel, PET technologists, computer support personnel, equipment maintenance contracts (cyclotron, chemistry modules, gas chromatographs, HPLCs, PET scanners, computer cluster, etc.), chemistry supplies (including precursors), sterility and pyrogen tests, PET transmission and/or CT scans, supplies for PET scans such as IV solutions and catheters, daily PET scanner quality control, image reconstruction on a dedicated computer cluster, storage and backup of reconstructed PET data, and processing for fully automated production of binding potential images. Costs for maintaining and overseeing the cGMP compliant PET radiochemistry lab (including pyrogen testing and sterility testing for each production run, weekly viable particulate and monthly total particulate monitoring, annual or bi-annual calibration and certification of all the equipment that is involved in production for human studies) are also included. These include costs for yearly equipment calibrations (HPLCs, gas chromatographs, chemistry modules, hot cell air quality, sterile hoods, pH meters, etc.) that are performed by outside independent firms.

For studies with Arterial line/Metabolites: In this study, arterial blood sampling will be performed with metabolite analysis. The additional charge covers the physician fee for placement of the arterial line, nurse oversight of the line for the duration of the study, additional supplies needed for continuous and discrete arterial blood sampling and laboratory staff and supplies for HPLC and gamma counter analyses as well as data processing.

For studies with PET scans only: The basic PET study cost includes PET technologists, computer support personnel, equipment maintenance contracts (computer cluster, etc.), PET transmission and/or CT scans, supplies for PET scans such as IV solutions and catheters, daily PET scanner quality control, image reconstruction on a dedicated computer cluster, storage and backup of reconstructed PET data, and processing for fully automated production of physiological images.

Clinical Services: A physician and/or nurse is available to handle any urgent medical issues that may arise while a subject is at the Yale University PET Center. For an additional fee, the PET Center offers physician services such as supervision of pharmacologic studies, physical examinations, medical clearance, as well as Physician or Research Assistant services for subject screenings.

The Yale PET Center Resources

The state-of-the-art 16,000 sq. ft. PET Center was opened at Yale University in July 2005. The PET Center has a GE PETtrace cyclotron, with targetry for producing C-11, F-18, N-13 and O-15 radioisotopes. Chemistry modules are available for the production of a wide variety of radiotracers. The Center has 6 scanners. 3 for clinical imaging (HR+, HRRT, mCT-X PET/CT) and 3 for small

animal imaging (2 Focus-220, Inveon PET/CT). Two laboratories for blood and metabolite analyses are available. The Center also has an image analysis laboratory for investigators, with several workstations running image analysis software applications. To date, over 8,000 administrations of PET radiopharmaceuticals as part of quantitative *in vivo* PET studies have been performed with over 100 different radiopharmaceuticals, 43 of which have been used in human studies.

The details for each component of the resources related to this proposal are listed below.

Laboratories:

The laboratory resources within the Yale University PET Center consist of four laboratories: 1. PET radiochemistry laboratory; 2. PET radioligand quality control (QC) laboratory; 3. organic chemistry laboratory; 4. blood and metabolite analysis laboratory.

1. PET radiochemistry laboratory: The radiochemistry laboratory complex at the PET Center, Yale University School of Medicine, is fully equipped for radiotracer synthesis with 6 mini hot cells, 6 full size hot cells from Comecer and a process chemistry cabinet (ProCab) from GE. The ProCab is fitted with several chemistry process modules, including a $[^{11}C]CO_2$ purification module capable of purifying and delivering $[^{11}C]CO_2$ at a controlled flow rate for various chemistry applications, a $[^{11}C]CO$ module for conversion of $[^{11}C]CO_2$ to $[^{11}C]CO$, a $[^{11}C]$cyanide module for conversion of $[^{11}C]CO_2$ to $[^{11}C]HCN$. Remote-controlled or automated synthesis modules from GE are installed in the various hot cells for either dedicated or diversified synthetic processes. These automated modules include one MicroLab $[^{11}C]$methyl iodide synthetic device, one FxC module and one FxC-pro module for $[^{11}C]$methyl iodide and [11C]methyl triflate production, methylation, purification and final product formulation, one FxN module and one FxNpro module for production of F-18 labeled compounds through nucleophilic reaction, one FxE module for making F-18 labeled ligands using electrophilic chemistry, one MX module for FDG production, and two other modules for dedicated production of $[^{15}O]$water and $[^{13}N]$ammonia. In addition, there is also one Bioscan AutoLoop for performing loop-based chemistry in the production of C-11, and Advion's microfluidic module for F-18 labeled compounds. Various home-made modules can also be used for the productions of labeled compounds using $[^{11}C]CO_2$, $[^{11}C]CO$ and $[^{11}C]HCN$. A total of ten preparative HPLC systems complete the capability to produce and purify radiolabeled ligands. A total of 6 Capintec dose calibrators are installed in the full-size hot cells and on the bench for measurement of radioactivity. A microwave oven from Resonance Instrument can be used in radiolabeling with $[^{18}F]$fluoride. Various other equipment/instruments includes a drying oven, a glove box for preparation of moisture-free and oxygen-free reagents and solutions, refrigerators/freezers for sample storage, pH meters, vacuum pumps, vortex, sonicators, filtration equipment, water purification system, and others.

2. Quality control laboratory:

The quality control laboratory, located in a room separated from the main radiochemistry laboratory, is equipped with four Shimadzu analytical HPLC systems including four HPLC pumps, two autosamplers, one photodiode array (PDA) detector, three dual channel UV detectors, four radioactivity detectors and computers running the Class VP HPLC control/data acquisition software. There are one Shimadzu model 2014 gas chromatography (GC) system for residual solvent analysis that includes autosampler and dual injectors and one Bioscan AR-2000 TLC scanner. In addition, a Varian LC/MS system is in place for quality control and analysis of product and byproducts. A laminar flow hood provides the capability for performing sterile preparations and compounding of radiopharmaceuticals. Also located in this lab are one dose calibrator for measuring radioactivity and equipment for pyrogen testing of radiopharmaceuticals.

3. Organic chemistry laboratory:

Two rooms with a total of 1500 square feet of space in the Laboratory Medicine and Pediatrics (LMP) building are dedicated to organic chemistry and are equipped for the purpose of developing new synthetic strategies for C-11 and F-18 labeled radiotracers and to synthesize the unlabeled precursors required for radiotracer development and production. There are a total of six fume hoods for performing chemical reactions. Major instruments includes two HPLC systems for analysis of precursors and other synthetic compounds, refrigerators for reagents and samples storage, vacuum pumps, drying ovens, rotary evaporators, melting point apparatus, and others.

4. Blood and metabolite analysis laboratory:

Two laboratories for plasma analysis are adjacent to the PET Imaging suites, with pass-through doors to allow direct passing of samples. These labs include four Perkin Elmer Wizard gamma counters, two balances, four centrifuges, and one blood glucose analyzer. Three HPLC systems are dedicated to the analysis of plasma samples for unchanged radiotracer and radioactive metabolites, enabling generation of input functions required for kinetic analysis and image quantification. Each HPLC system consists of two Shimadzu pumps capable of delivering gradient mobile phase, one control module, one Rheodyne manual injector equipped with a 5 mL sample loop, one Shimadzu variable wavelength UV-vis detector, one Raytest radioactivity detector, and one fraction collector. HPLC system control was provided by the Shimadzu Class-VP software.

As appropriate, devices are connected to the internal computer network (some via a terminal server) to allow direct reading of the data by IDL programs on the Linux machines.

Animal:

Adjacent to the PET facility are three animal housing rooms, with one room dedicated to rhesus monkeys (800 ft^2), and one to baboons (550 ft^2), and one to rodents (115 ft^2). There are three dedicated animal procedure rooms. These rooms are used for procedures (intubation, placement of intravenous and intra-arterial lines, PK sampling, port maintenance), and animal training and testing. There is also a fourth swing procedure room space (134 ft^2) that can be converted to animal housing, if needed. There is also a dedicated animal environmental enrichment room. Animal studies share clinical research resources including access to the PET scanners, use of all clinical radiotracers and technical support for input function measurement, protein binding assays and metabolite assays. In addition, many experimental radiotracers are synthesized exclusively for animal studies.

Two dedicated PET animal imaging areas are adjacent to the PET Center and to our current animal housing area. Both areas have dedicated scanner space and a control room. One room contains one Focus 220 PET scanner attached to a lifter unit which permits the scanner to be tilted to 90º. This scanner room is adjacent to a hot lab for dose dispensing and blood sample analysis. A second scanner room contains the second Focus-220 and the Inveon rodent PET/CT scanner.

Computer:

PET images are converted to DICOM format and saved on a 40 TB disk farm. The disk farm is backed up to tape nightly. Image processing is performed on one of 6 Linux (Redhat WS4) workstations housed in a data processing room connected to the network with NFS mounts to the disk array. These systems may be used at their consoles or over the network via X windows. Image data are accessed via the HAVEN image database using scripts and programs employing the commercial programs IDL and MEDx. All data are identified with a code created at the time of the subject's first PET scan. Human subject identification can only be obtained from password-restricted access to the

HAVEN database. Programs and scripts developed for image processing include PET-MR image registration, region-of-interest placement (on PET or MR), time-activity curve creation, input function creation (see Metabolite lab, above), mathematical modeling routines to create parametric images of flow, metabolism, binding potential, etc. and partial volume correction.

Office:

The scientific and professional staff has offices in the Laboratory for Medicine and Pediatrics (LMP) and in the PET Center.

Others:

Various equipment/instrument in the MR Center and Chemistry Department of Yale University are open to the PET Center personnel. These include the NMR facilities, GC-MS instrument, and other analytical equipment.

Major equipment

Cyclotron: A GE PETtrace cyclotron for radioisotope production is located in the lower level of the PET Center. The cyclotron uses 16.5 MeV protons and 8.4 MeV deuterons to produce radioisotopes. A total of six targets are mounted in the cyclotron: two C-11 targets, two F-18 targets for production of [^{18}F]fluoride and [^{18}F]fluorine, one O-15 target and one N-13 target.

PET Scanners: The Yale PET Center has one whole body PET/CT scanner (Siemens mCT-X, with 109 PET slices with resolution of ~ 5x5x5 mm resolution, 128-slice CT funded by a Shared Instrumentation Grant, 1S10RR029245, PI: R. Carson), one whole body PET-only scanner (Siemens HR+ with 32 rings and 63 planes with a resolution of ~ 5 x 5 x 5 mm at center of field of view), one brain-dedicated scanner (Siemens High Resolution Research Tomograph (HRRT), 104 rings, 207 slices with resolution of better than 3 x 3 x 3 mm), and two small animal PET scanners (Siemens Focus 220, 48 rings, 95 slices with a resolution of ~ 1.4 x 1.4 x 1.4 mm at center field of view), and one small animal PET/CT (Siemens Inveon, 159 slices, with 0.8 mm slice separation, axial coverage of 127 mm, transaxial field-of-view of 100 mm, resolution < 1.5 mm, peak sensitivity > 9%). Adjacent to each scanner room are patient prep rooms. The HR+ has a SUN workstation dedicated to image acquisition, reconstruction, and archiving. The HRRT system acquires list-mode data. The HRRT list-mode data files are transferred over the local Gigabit network (behind a hardware firewall) to a dedicated Linux cluster with 74 nodes and 264 processors (3.0-3.2 MHz) ~ 20 TB of disk storage. Images are reconstructed with the MOLAR algorithm (Motion-compensation OSEM List-mode Algorithm for Resolution-recovery Reconstruction). Subject motion information is collected with a Vicra (NDI, Canada), which records head motion at a rate of up to 20 Hz. These are stored in a time-synced file and used by MOLAR to correct head motion. The mCT, Focus 220, and Inveon scanners also acquire list-mode data, which is also used to reconstruct images using the manufacturer's software. Continuous bed motion and dual-gated acquisitions are features of the Focus 220. Respiratory and cardiac gating are available on the mCT and Inveon.

Yale University PET Center Protocol Initiation Form

PI: _____

Email: _____

Phone: _____

Protocol Title: _____

_____

Protocol Short Name (generated in PET Center):_____

HIC#: _____ **IACUC#:** _____

RA:_____**Phone:**_____

Email:_____

Other

Personnel:_____ **Email:**_____

_____ **Email:** _____

Scheduler:_____ **Phone:**_____

Email:_____

Will medical / nursing / vet staff be provided by PI? If yes, please provide:

Name:_____

Phone_____ **Email:** _____

Number of subjects projected to be scanned:_____

Expected scanning start date:_____ **Expected scanning end date:**_____

Scanner to be used:

___ **HRRT (Hi Resolution Brain Scanner)**

___ **HR+ (Brain or Whole Body)**

___ **mCT (Brain or Whole Body with Hi Resolution CT)**

___ **Focus-220 (Animal Scanner for Primate or Rodents)**

___ **mCT or HR+ (No Preference)**

___ **HRRT or HR+ (No Preference)**

___ **Any Human Scanner will suffice**

___ **PET Center decides**

Tracer Name: _____

Tracer Source:

___Made by Yale PET Center

___Purchased/delivered by outside source Source:_____

Contact Name:_____ Phone Number:_____

Dose delivery time window:

___Metabolites ___Arterial line ____PK Samples

Pharmacologic Compound (i.e. cold non-radioactive drug), if applicable:

_____

Number of scans per subject and any time/day restriction, if required, examples:

- 2 scans, 7 days apart, with both injections before 12 PM
- 2 injections on one day with break of at least 90 min between scans

_____

_____

PTAEO and contact info for person responsible for billing [name, email and phone]**:**

_____

PTAEO Expiration Date:_____

____ Split Charges between 2 accounts

Second PTAEO number: _____Expires:_____

Billing Notes:

_____

PET Center issuing subject payments? Yes ___No___

PTAEO for subject payments:_____ Expires:_____

These items must be on file at the PET Center before scan scheduling is allowed to begin:

- ✓ **Y-NHH Radiation Safety Committee approval letter (human studies) and, if applicable, FDA 2915 Form for human studies with > 31 subjects)**
- ✓ **Yale University RSC approval letter**
- ✓ **Electronic copy of approved protocol**
- ✓ **Electronic copy of approved consents (human studies)**
- ✓ **HIC (IRB) Approval Letter**

Funding Agency:_____

Funding Mechanism:_____

Yale University PET Center Subject Information Form

Protocol Code: _____ HIC#: _____

PI: _____

PI Immediate Contact Phone Number[1]: _____

PET Scan Date: _____ Subject Arrival Time: _____

Subject Legal Last Name (print)**: _____**

Subject Legal First Name (print)**: _____**

MRI TR#: _____ Scanset Number:_____

DOB: _____ Ethnicity[2]: _____

Subject Age at PET Scan Date_____ Known Allergies_____

Gender: Male __ Female __ Subject Study ID: _____

Primary Dx: _____ Secondary Dx [if any]**: _____**

Height: _____ meters Weight: _____ kg

Subject Contact Phone Number: _____

Research Staff Accompanying Subject: _____

Please include pertinent medical labs or history and progress notes

Lab & EKG results if study uses arterial lines or pharmacologic compounds (cold non-radioactive drug)

Current Medications:_____

Known Allergies:_____

PET Center to consent with Yale form on day of PET scan? Y___ N ___

Vegetarian Lunch: Y___ N ___

Subject Travel Arrangements:_____

IMPORTANT: For the last scan of the day, a research staff member must be present a minimum of 15 minutes before the scheduled end of scan until the subject leaves the PET Center.

Subject may be required to be at the PET Center for a few hours longer than the planned scanning session, should there be delays due to issues with radiotracer production, arterial line insertion, or PET scanning equipment.

Send to PET.scheduling@yale.edu or fax to 203.785.2994, along with a valid, signed consent, a minimum of **3 business days before the scan is scheduled** or you risk cancellation.

[1]Will only be used if absolutely necessary while subject is on-site at the PET Center.
[2]American Indian or Alaskan, Asian, Black (Not of Hispanic Origin), Hispanic or Latino, White (Not of Hispanic Origin), Native Hawaiian or Other Pacific Islander, Other / Unknown

Guidelines for PET Center Research Subjects on Scan Days

Please Advise Subject To:

- Not wear clothing with hoods as this interferes with setup.
- Remove jewelry and body piercings prior to scan day.
- Refrain from wearing tight fitting clothing (short sleeves are best). Warm, comfortable and loose fitting clothing is advised.
- Carry only the minimum amount of cash they will need (e.g. transportation costs).
- For PET scans that will require arterial lines, please reiterate to the subject that they are to abstain from physical exercise 24-48 hrs after scan day.
    - Advise the subject to drink at least 2-3 glasses of water the night prior to and after their PET scan.
- If a urine sample is required on scan day, please instruct the subject that they will need to provide urine first thing upon their arrival.
    - All females of child-bearing potential will need to provide a urine sample for a pregnancy test.
- If an ECG(s) will be performed, please instruct the subject to refrain from wearing lotions as this may interfere with adhering the cardiac leads.
- A DVD player is available for entertainment during down time. Please inform subjects that they may bring any DVD's, books, etc. for use during down time.
    - The PET Center is not, however, personally responsible for any lost items.

Please inform subjects that there is a possibility that scan days could lengthen, should any equipment failure occur

IMPORTANT:

***If your subject is running behind schedule, please contact the PET Center Nursing Staff at: (203) 491-8438.**

***We will notify you of any cancellations or major delays. Please provide us with a contact number for status updates.**

PET Center Guidelines for Research Assistants

- All study specific medications that will need to be administered (or will potentially need to be administered) to a subject should be given to a Research Nurse to keep locked up in the medication box until time of administration (examples include cold non-radioactive drugs, and/or antidotes such as valium).

- For pharmacologic studies (those using cold non-radioactive drug in addition to radiotracer), RAs must also provide subject medical records on day of scan (including laboratory and EKG results).

- Any study medication planned for administration under the protocol, or medication given to a subject for symptoms such as a headache, sore wrist, anxiety, etc., must be ordered by a medically responsible PI or Medical Director and administered by a nurse or physician.

- It is important to be familiar with the telephone paging system in the event that you are in a room with a subject who is in distress. Each PET Center room has a phone and a blue card taped above the phone with paging instructions and room numbers.

- Please be sure to tell your subjects, *not* to void when they arrive at the PET Center waiting room. It is very important that we get a urine specimen prior to arterial lines and IV's.

- Please use the clipboard in room 206 to sign in and out and leave a cell phone # in the event we need to contact you.

- Research Assistants who need Radiation Safety Training must contact Maria Corsi (maria.corsi@yale.edu) to schedule a training session

Radiation Safety Training Scheduling Procedures

- Supervisor (or designee) will send an email to the Chief PET Technologist (maria.corsi@yale.edu) identifying staff who will require PET-specific Radiation Safety Training. Staff member requiring training will also be cc'd on email.

  Email will include:

  Protocol short name/ HIC number

  Staff member's name/ title/ departmental affiliation/ facility/ direct supervisor

  Staff member's responsibilities (relative to the PET Center)

  Training completion "due-by" date

- The Chief PET Technologist will forward all information to June Tamkin-Price (or assigned designee), cc'ing the individual who requires training. The trainer and trainee will be encouraged to communicate meeting times and location directly to each other, cc'ing the Chief PET Technologist

- Additionally, cancellations and rescheduling must also be made directly between the trainer and the trainee, cc'ing the Chief PET Technologist

- Dosimeters issued are required to be kept onsite at the PET Center, in a previously designated area. When possible, please let us know when the dosimeter badge is no longer needed so that it can be discontinued.

- A digital copy of training records will be kept on the Yale University PET Center website at Radiation Safety / PET-specific Radiation Safety Training / staff training

- This procedure will enable timely staff training and allow access to the PET Center

Yale University PET Center Subject Discharge Instructions

NOTE: SUBJECTS WILL BE GIVEN A POST-SCAN INSTRUCTION SHEET WHEN DISCHARGED FROM PET CENTER

Subject ID: _____ Date: _____

Discharge Instructions

This form provides you with post scan instructions. Please do not hesitate to call one of the physicians listed below for any questions. Please take this form with you in case you need further care.

☐ **Nuclear medicine discharge instructions**:

1. You received a nuclear medicine injection today and there is a very slight possibility that you could activate a radiation device. Please remember that you were given a blue, "security and law enforcement notification card," to present in the event it is needed.
2. You had an intravenous catheter(s) inserted into your R/L forearm vein; R/L hand vein; other_____. You may remove the band aid from the site in the morning. Please be advised that a small amount of bruising is normal. However, if you experience any swelling, redness or pain at the site, you should notify one of the physicians listed below.
3. You had blood drawn for today's study. Please drink plenty of fluids to help restore blood volume and prevent lightheadedness. Extra fluid aides in removing the radioisotope as well. Therefore please empty your bladder as frequently as possible.
4. You did/did not have a study medication. If you received medication, it is listed here: _____. Please notify the physicians listed below if you notice any of the symptoms listed on your consent form, such as: nausea, vomiting, lightheadedness, fainting, racing heart, headache, etc.

☐ **Arterial line discharge instructions: You had your R/L artery accessed, therefore please follow these instructions:**

1. No bending affected arm or wrist for 4hr.
2. Refrain from strenuous exercise, reaching, or lifting heavy objects (no more than 5 lbs,) for 48 hours.
3. Refrain from repetitive movements in the affected wrist for 48 hr.
4. Keep elastic wrap in place until bedtime and then remove. Check site, and call the MD's listed below if there are any issues such as, pain, bleeding, swelling, numbness, tingling, and change in color or temperature.
5. Keep transparent, (clear) dressing clean and dry for 48hr, (wrap in plastic bag for showering or hold arm outside of shower.)
6. You may remove the transparent dressing in 48hr, but do not submerge wrist in water (no dishwashing, bathtub nor swimming,) for another 24hours.

IMPORTANT

If you experience any unusual bleeding or swelling at the site of the arterial line, you should:

- **Immediately apply continuous pressure at the site with your fingertips and a clean towel and/or go directly to an urgent center or emergency room and bring these instructions with you.**
- **Call: Dr. David Matuskey at 203-370-1403 (pager) or Dr. Ming-Kai Chen 203-766-4241 (pager) You will need to punch in your tel. number with area code followed by the, "#," sign.**

Signature of research subject: _____

Signature of PET Center nurse or MD: _____

Please Note: Discharge instructions must be reviewed with subject, and subject must verbalize understanding prior to signing. A Signed copy to must be placed in subject folder. Pet Center Nursing Discharge Instruction Sheet/v:18Feb2015

Yale University PET Center Data Repository

Request for Healthy Control PET Data

Date: _____

Investigator Name: _____

Department/ Academic Appointment: _____

_____

Phone Number: _____**Email Address:** _____

Purpose of Data Request/Research Objective: _____

_____

_____

_____

_____

Healthy Control PET Data Requested:(please provide/circle the following information needed)

Radiotracer Name(s):_____

Tracer Administration Information: (e.g., radiation dose, specific activity, purity)_____

_____

Scanning Parameters: (time of injection, length of scan (min), date(s) when scan(s) were performed)___

_____

Arterial Line Blood Data: (e.g. metabolite correction plasma curve, whole blood total radioactivity curve, plasma free fraction, etc.)_____

_____

Please Circle Data Needed:

Type of injection (infusion; bolus)
Scanner **(**HR+, HRRT, PET/CT, m/CT, MR)
Type of Image Data (raw PET data, DICOM reconstructed images, parametric images, calculated regional values)
Demographics (age, gender, race, height, weight, education level)_____

Neuropsychiatric Measures: (e.g., CogState**,** Barrett's impulsivity measures, Neo Inventory)_____

_____

_____

Other Considerations:_____

_____

_____

_____

_____

I agree that the information I have requested will only be used for the research purpose stated in this Request Form and its accompanying documentation. I agree that I will use only the information necessary for the research purpose described. I will protect the confidentiality and security of this information while it is in my possession.

_____**Date:**_____

Signature of Investigator Requesting PET Data

SEND PET DATA REQUEST FORM TO: Amy Turner (amy.turner@yale.edu)

Form Version: 11/11/2015