Validation of PET/MRI integrated system acquisition for cardiac applications

NCT02062008

Document Date: December 12, 2016

Study Application (Version 1.5)

1.0 General Information

***Enter the full title of your study:**

Validation of PET/MRI integrated system acquisition for cardiac applications

***Enter the study number or study alias**

Validation of cardiac PET MR
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add Department(s)

2.1 List the departments associated with this study. The Principal Investigator's department should be Primary.:

Primary Dept?	Department Name
◆	**UCSF** - *147100* - M_Radiology

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Hernandez Pampaloni, Jose Miguel MD, MD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Acevedo-Bolton, Gabriel,PhD
Other Investigator
Bacharach, Stephen
Other Investigator
Behr, Spencer C
Other Investigator
Botvinick, Elias H
Other Investigator

Dae, Michael W
Other Investigator
Gerstenfeld, Edward P M.D.
Other Investigator
Guccione, Julius M Ph.D.
Other Investigator
Haraldsson, Henrik
Other Investigator
Hernandez Pampaloni, Jose Miguel MD, MD
Co-Principal Investigator
Hope, Michael D
Other Investigator
Hope, Thomas A, MD
Other Investigator
Kanaya, Alka M
Other Investigator
Liu, Jing PhD
Other Investigator
Mukai, Kanae
Other Investigator
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Naeger, David M
Other Investigator
Ordovas, Karen G MD, MAS, MD
Co-Principal Investigator
Saloner, David A Ph.D., PhD
Other Investigator
Yeghiazarians, Yerem
Other Investigator

B) Research Support Staff

Gao, Kenneth T
Research Assistant
Lorca, Maria Clara
Research Assistant
Tao, Dora H
Research Assistant
Verdin, Emily F
Research Assistant
Wong, Samantha A
Research Assistant

3.3 *Please add a Study Contact:

Hernandez Pampaloni, Jose Miguel MD, MD
Ordovas, Karen G MD, MAS, MD

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Qualifications of Key Study Personnel

4.1 November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website.**

List the study responsibilities and qualifications of any individuals who qualify as Key Study Personnel (KSP) at UCSF and affiliated sites ONLY by clicking the "Add a new row" button. This information is required and your application will be considered incomplete without it.

KSP Name	Description of Study Responsibilities	Qualifications
Dr. Ordovas, Karen G MD, MD	Co-Principal Investigator,	Radiologist with large expertise in MRI cardiac applications
Dr. Saloner, David, PhD	Other Investigator,	PhD Physiscit. Expert in MRI applications in the cardiovascular system.
Lorca, Maria Clara	Research Assistant	Post- Doctoral Fellowship
Hernandez Pampaloni, Jose MD, PhD, MD, PhD	Co-Principal Investigator	Radiologist. Chief of Nuclear Medicine at UCSF with extensive published work in cardiovasular PET imaging.
Behr, Spencer, MD	Other Investigator,	Radiologist with expertise in cross-sectional imaging
Botvinick, Elias H	Other Investigator,	Cardiologist. Expert in Nuclear Cardiology
Liu, Jing PhD, PhD	Other Investigator,	PhD, Physicist. Expertise in cross-sectional physics
Dae, Michael W	Other Investigator,	Radiologist. Expert in nuclear cardiology
Acevedo-Bolton, Gabriel, PhD	Other Investigator,	PhD
Dr. Guccione, Julius, PhD	Other Investigator,	Bioengineer
Dr. Hope, Michael MD, MD	Other Investigator,	Chest Radiologist with

		expertise in MRI applications in the cardiovascular field
Naeger, David M	Other Investigator,	Chest Radiologist. Expertise in PET imaging and cross-sectional imaging of the chest.
Dr. Yeghiazarians, Yerem MD, 1995	Other investigator	Cardiologist. Interventional Cardiologist
Dr. Kanaya, Alka MD	Other investigator	Cardiologist
Hope, Thomas A, MD	Other investigator	Radiologist with experience in PET and cross-sectional imaging
Dr. Gerstenfeld, Edward P M.D. , MD	Other investigator	Cardiologist. Chief of cardiac electrophysiology
Dr. Haraldsson, Henrik PhD	Other investigator	Physicist
Bacharach, Stephen	Other Investigator	Physicist. Extensive experience in applications of PET imaging in cardiovascular disorders, including quantification of myocardial blood flow
Mukai, Kanae	Other investigator	Advanced Cardiac Imaging fellow

5.0 Initial Screening Questions - Updated 9/13

(Note: You must answer every question on this page to proceed).

If you are converting to the new form, check questions 5.4, 5.6, 5.7, 5.8 and 5.10 before saving and continuing to the next section.

5.1 * Application type:

- (•) Full Committee
- ( ) Expedited
- ( ) Exempt

5.2 * Risk level (Help Text updated 9/13):

- ( ) Minimal risk
- (•) Greater than minimal risk

5.3 * Subject contact:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

5.4 * Funding (past or present):

- (•) Funded or will be funded (external sponsor, gift, program or specific internal or departmental funds)
- ( ) Unfunded (no specific funds earmarked for this project)

○ Unfunded student project

5.5 * The Principal Investigator and/or one or more of the key study personnel has financial interests related to this study:

○ Yes ◉ No

If **Yes**, the Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

5.6 * This is an investigator-initiated study:

◉ Yes ○ No

5.7 * This study ONLY involves retrospective records review and/or identifiable biospecimen analysis:

○ Yes ◉ No

5.8 * This is a clinical trial:

◉ Yes ○ No

Clinical Trial Registration
"NCT" number for this trial:

NCT02062008

5.9 * This is a multicenter study:

○ Yes ◉ No

5.10 * This application involves the study of unapproved or approved drugs, devices, biologics or in vitro diagnostics:

◉ Yes ○ No

5.11 * This application involves a Humanitarian Use Device:

◉ No
○ Yes, and it includes a research component
○ Yes, and it involves clinical care ONLY

5.12 * This study involves human stem cells (including iPS cells and adult stem cells), gametes or embryos:

◉ No
○ Yes, and requires CHR and GESCR review
○ Yes, and requires GESCR review, but NOT CHR review

5.13 * This is a CIRB study (e.g. the NCI CIRB will be the IRB of record):

○ Yes ◉ No

5.14 * This application includes a request to rely on another IRB (other than NCI CIRB):

○ Yes ◉ No

Note: If this request is approved, the CHR will **NOT** review and approve this study. Another institution will be the IRB of record.

6.0 Funding

6.1 Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor: **Note: we require only a P Number *OR* an A Number for funding coming through UCSF. Please avoid these common errors in funding documentation:**

- **DO NOT add the A Number if a P Number was already provided OR update the A Number field when a new funding cycle begins. The IRB does NOT use this information or want these changes made.**
- **DO NOT add a grant continuation as a new funding source.**

External Sponsor:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	GE Medical Systems	04	UCSF	Grant	P0501481	

Sponsor Name:	GE Medical Systems
Sponsor Type:	04
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	CA-0050676
Awardee Institution:	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
UCSF RAS "P number" or eProposal number:	P0501481
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	
PI Name: (If PI is not the same as identified on the study.)	
Significant Discrepancy:	

Gift, Program, or Internal Funding (check all that apply):

- [ ] Funded by gift (specify source below)
- [ ] Funded by UCSF or UC-wide program (specify source below)
- [ ] Specific departmental funding (specify source below, if applicable)

List the gift, program, or departmental funding source:

6.2 If you tried to add a sponsor in the question above and it was not in the list, follow these steps:

- **If funding has already been awarded or the contract is being processed by the Office of Sponsored Research (OSR) or Industry Contracts Division (ICD), your sponsor is already in the system and the project has an eProposal Proposal or Award number. Check with your department's OSR Staff or ICD Officer to ask how the sponsor is listed in the UC sponsor list and what the Proposal or Award number is. Click here to find your OSR staff and here to find your ICD staff.**
- **If your sponsor is not yet in the list, enter it in the box below.**

- ( ) Sponsor not in list

Only if your sponsor is not yet in the list, type the sponsor's name:

If the funding is administered by the UCSF Office of Sponsored Research, your study will not receive CHR approval until the sponsor and funding details have been added to your application.

6.3 * This study is currently supported in whole or in part by Federal funding OR has received ANY Federal funding in the past (Help Text updated 9/13):

- ( ) Yes
- (•) No

If **yes**, indicate which portion of your grant you will be attaching:

- [ ] The Research Plan, including the Human Subjects Section of your NIH grant or subcontract
- [ ] For other federal proposals (contracts or grants), the section of the proposal describing human subjects work
- [ ] The section of your progress report if it provides the most current information about your human subjects work
- [ ] The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

7.0 Sites

7.1 Institutions (check all that apply):

- [x] UCSF
- [x] China Basin
- [ ] Helen Diller Family Comprehensive Cancer Center
- [ ] Mission Bay
- [ ] Mount Zion
- [ ] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Blood Centers of the Pacific (BCP)

- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno (Community Medical Center)
- [ ] Gallo
- [ ] Gladstone
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)

7.2 Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project (Help Text updated 9/13):

- [ ] Other UC Campus
- [ ] Other institution
- [ ] Other community-based site
- [ ] Foreign Country

List the foreign country/ies:

7.3 Check any research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program

8.0 Study Design

8.1 * Study design (Help Text updated 9/13):

The goal of this study is to understand how simultaneous PET/MR acquisition can provide novel qualitative and quantitative information to guide clinical intervention and predict prognosis of patients with risk factors for the development of coronary artery disease, or with diagnosis of cardiovascular ischemic or inflamatory disorders.

Patients required to have a clinical cardiac FDG PET or PET/CT imaging study as part of standard of care, to detect myocardial viability or a cardiac inflammatory process will be enrolled in the study. After the initial acquisition of the clinical study patients will be immediately imaged in the PET/MRI system, with no additional administration of any radiopharmaceutical. The main purpose of the study would then be to compare the infomration proveided form the clinical PET/CT with the one from the simultaneous cardiac PET/MRI.

8.2 If this is a clinical trial, check the applicable phase(s) (Help Text updated 9/13):

- [ ] Phase I
- [ ] Phase II
- [ ] Phase III
- [x] Phase IV

9.0 Scientific Considerations

9.1 Hypothesis (Help Text updated 9/13):

This study has a hypothesis:

(•) Yes ( ) No

If yes, state the hypothesis or hypotheses:

We hypothesize that simultatenous acquisition of cardiac PET/MRI can could provide some other benefits in comparison to stand alone scanners.

– In a hybrid system, real-time MR-based motion detection and correction could be applied since cardiac and respiratory gating can be image-based without external sensors. This could allow partial-volume correction and event-based correction of patient motion during the PET acquisition.
-Combined metabolic information provided by FDG and structural information offered by MRI can help to better define the extent , location and siginficance of infarcted myocardium or viable tissue, with special significance for non-transmural or transmural lesions.
– The lack of exposure to ionizing radiation and iodinated contrast agents makes hybrid PET/MRI attractive when compared with PET/CT.
– Both cardiac MRI and PET examinations can be rather time consuming. Thus, improvements in patient compliance as a result of reduced scan time could be significant, particularly in patients with dyspnea due to heart failure who have difficulty holding their breath during MRI acquisitions.
– Increased patient throughout based on reduced scan times is also likely to be cost-effective.

9.2 * List the specific aims:

· To compare regional myocardial uptake of FDG on images obtained on a standard PET camera with the new PET/MR camera, in patients with and without overt diagnosis of ischemic coronary artery disease.
· To compare viability maps obtained with cardiac MR images and FDG-PET for delineation of myocardial infarct core and border zone, in patients with coronary artery disease.
· To correlate MRI myocardial strain with relative myocardial FDG uptake in patients with a previous myocardial infarction, referred for a clinical myocardial viability study.
· To interrogate if simultaneous acquisition of cardiac PET and viability cardiac MR differ from acquisitions obtained independently, with special focus on attenuation correction methods.
· To combined MRI scar map with FDG-PET uptake in patients with cardiac sarcoidosis and myocarditis.
· To evaluate cardiac strain and myocardial scar burden in obese patients with and without diabetes.

9.3 Statistical analysis:

Correlation coefficient and Bland Altman plots will be applied to evaluate the agreement between linear variables obtained from PET and cardiac MRI.

9.4 If this study has undergone scientific or scholarly review, please indicate which entity performed the review:

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Center (CRC) advisory committee
- [x] Departmental scientific review
- [ ] Other:

Specify **Other**:

10.0 Background

10.1 Background:

Background

Magnetic resonance (MR) imaging and positron emission tomography (PET) have been clinically available for more than 20 years and have evolved into highly valuable and versatile tools in diagnostic imaging. Since their first introduction, both imaging modalities have undergone a largely independent evolution in regard to technological development and clinical application. Nevertheless, since the first implementation of these inherently different imaging modalities, the idea of combining both into hybrid systems to complement each other has emerged.
Simultateous acquisition of cardiac MRI and PET images has multiple potential clinical applications, particularly in patients with coronary artery disease and cardiomyopathies. While cardiac MRI provides high spatial resolution, and precise characterization of flow and function, PET imaging adds metabolic information that can be coregistered with MRI images.
The importance of identification and quantification of the border zone of an infarct has been emphasize in recent cardiac imaging publications. The extent of border zone is a strong predictor of adverse left ventricular remodeling and lethal arrhythmias after an MI. In addition, it has been described that residual ischemia after MI is a strong predictor of adverse outcomes. However, the relationship between ischemia and border zone is not clearly understood. We have previously demonstrated the potential of chronic low dose vasodilator therapy to decrease the volume of border zone over time, a finding that suggests a potential role of combined high resolution scar and perfusion mapping in predicting response to specific treatment strategies in ischemic heart disease. In addition, combined PET MR acquisition may allow for assessment of any associations between border zone ischemia and myocardial strain, which may enhance our understanding of myocardial hybernation, and provide potential goals for treatment strategies.
Compared to PET, MR has the ability to assess whether a region of ischemia and scar is transmural or not, and to map areas of core and border zone infarct. The relationship between ischemia and border zone may be an important consideration in determining whether tissue in the border zone can be salvaged.
In patients with cardiac sarcoidosis and myocarditis, it is well established that abnormal cardiac MR delayed enhancement and FDG uptake are important features for diagnosis, prognosis and for guiding therapy. However, the mismatch between these abnormalities has not been interrogated. Quantification of delayed enhancement areas that do not correspond to FDG uptake could be a novel biomarker for quiescent or chronic disease, and may have important role in patient management.
Another area of potential application for combined PET-MR imaging is metabolic diseases and obesity. MRI has the ability to quantify myocardial strain and vessel wall abnormalities, which can be combined with PET information on cardiac metabolism and vessel wall information to aid on characterization of obesity-related organ damage. Combined FDG-PET acquisition with morphologic characterization of atherosclerotic plaque can also be combined with morphologic markers of inflammation, including atherosclerotic plaque components, and contrast enhancement with ferumoxytol, a marker of vessel wall inflammation.

10.2 Preliminary studies:

Positron emission tomography (PET) has contributed significantly to the advances in our understanding of cardiac physiology and pathophysiology for more than 20 years. In addition to being a powerful research tool in cardiology, recent technical development and improved availability facilitated also its routine clinical use in cardiology. PET is the most reliable non-invasive tool for the identification of
myocardial viability and also allows accurate assessment of myocardial perfusion and coronary artery disease (CAD), which is known to be the leading cause of mortality in adults. Imaging of myocardial viability with PET has been shown to identify heart failure patients who are at increased risk of death, which can be effectively reduced by surgical treatment.
Magnetic resonance imaging (MRI) has rapidly developed into a versatile tool for investigating cardiovascular diseases, especially for the evaluation of cardiac structure, assessment of ventricular function, and detection of myocardial infarction.Therefore, the combination of this technique without ionizing
radiation with PET is attractive in many applications.

To perform a combined analysis of sequential MRI and PET studies, images must be aligned accurately in the spatial domain. However, a particular challenge in cardiac
studies is that the three spatial dimensions must be supplemented with a time dimension in order to correct for continuous motion during respiratory and cardiac
cycles. Cardiac gating is routine in MRI and also possible in PET. Moreover, the integration of respiratory triggering is achieved using “navigators” (MRI) or list-mode acquisitions (PET). However, variable acquisition times between PET and MRI cause additional problems for exact timing of events. MRI scans are typically performed within few seconds during breath-holds while PET scans have a

minimum duration of 5 min. However, spatial co-registration is rarely addressed in studies using separate, sequential MRI and PET scans. Misalignment is mostly caused by significant patient motion, respiration, and cardiac contraction. The first two are very challenging, as they are involuntary and can produce irregular patterns. In their review, Mäkela et al. summarized the co-registration accuracy for intra- and intermodal cardiac applications. For alignment of repeated MRI acquisitions accuracies of 1.5–3.0 mm were reported. Co-registration
accuracy of repeated PET studies was on the order of 1.0– 2.5 mm. Finally, alignment of gated PET with gated MRI images showed an accuracy of 2.0±1.6 mm. In another study a misalignment of 2.8±0.5 mm was calculated using
thorax and lung surfaces. Co-registration of any data not acquired
simultaneously is therefore a major problem in inter- and intra-modal
examinations.

Assessment of heart failure
Ventricular function
Determination of LV function in gated PET studies is based on the use of partial volume effects. As the effective spatial resolution in clinical cardiac PET scans is approximately 6– 10 mm FWHM (full-width at half-maximum), changes in
wall thickness can be estimated in terms of changes in regional count rates during cardiac contraction. Using algorithm-dependent assumptions, such as homogeneous
tracer distribution over the myocardial wall, geometrical models can be used to estimate endo- and epicardial borders. This approach has been extensively implemented and validated in SPECT imaging and has also been
used in comparative MRI and PET studies. However, while being technically feasible, the accuracy of the assessment of global and regional LV function by PET
is limited by the low resolution of the PET compared to that of MRI. Here, MRI is clearly the modality-of-choice to quantitate cardiac function, such as volumes, mass, ejection fraction and regional wall thickening. Determination of LV function is essential for the diagnosis of heart failure and its prognostic value is well established. Therefore, its combination with any other imaging parameter is likely to provide incremental information.

Myocardial viability
Ischemic myocardium that is dysfunctional but viable has the potential for recovery of contractile function after revascularization. Evaluation of myocardial glucose utilization with 18F-FDG PET is considered as the most reliable tool to assess myocardial viability. Its quantitative nature allows assessment of the amount of viable tissue as a continuum from fully viable, through partially viable in the
areas of non-transmural infarction, to non-viable scar. Contrast-enhanced MRI appears to be a promising alternative capable of visualizing transmural distribution of viable and infarcted myocardium with excellent spatial resolution. Contrast-enhanced MRI of myocardial infarction is based on the delayed-enhancement technique using inversion-recovery prepared T1-weighted gradient-echo pulse
sequences after intravenous administration of Gd-DTPA. Infarcted myocardium appears enhanced relative to normal myocardium when imaged with a delay (typically 5–20 min) after intravenous injection of the contrast agent due to
different wash-out kinetics. A comparison of delayed-enhancement MRI with 18FFDG PET and 13NH3 in 31 patients with ischemic heart failure revealed that the location and extent of infarct scarring as delineated by delayed enhancement correlated very well with the non-viable segments from PET. The main source of difference between the methods was related to the presence of non-transmural
enhancement in regions that were viable on PET. This can be explained by the higher spatial resolution of MRI compared with nuclear imaging methods that makes delayed-enhancement suitable for the detection of small areas of subendocardial infarcts. An improved contractile performance after intervention is commonly considered as the gold standard for assessing myocardial viability,
although benefits of revascularization do not appear to be limited to improved function. In an initial study by Kim et al. in 41 patients with chronic ischaemic heart disease, dysfunctional segments with less than 25% of delayed enhancement were likely to recover after complete revascularization. In contrast, segments with more than 50% of delayed enhancement had a low probability (<10%) of
functional improvement. Comparable positive predictive values (73%) for functional recovery 6 months after revascularization were found for the lack of delayed enhancement (cut-off value less than 50% transmural scar) and the presence of preserved 18F-FDG uptake (cut-off value more than 50% of normal myocardium) as assessed by PET as the reference method to detect viable vs. nonviable myocardium. A recent meta-analysis of diagnostic studies indicated
that 18F-FDG PET has a higher sensitivity than delayed enhancement MRI (92% vs. 84%) in predicting functional recovery upon revascularization, while specificities were comparable (63%). The relatively low specificity of the techniques indicates that a substantial percentage of segments that are classified as viable by the imaging
techniques do not improve after revascularization. Although there are limited data on their combined use, adjunctive PET and MRI markers of viability, such as reduced
diastolic wall thickness, lack of contractile response to inotropic stimulation with a low dose of dobutamine, preserved epicardial rim of viable myocardium, and
preserved perfusion have been proposed to help refine the classification of dysfunctional segments as clinically viable or non-viable.

In addition to improved detection of viability, multimodal imaging approaches could contribute to the clarification of the complex pathophysiological basis underlying the LV dysfunction in ischemic heart failure. Non-invasive detection of viable myocardium in chronic LV dysfunction associated with CAD has important clinical implications for the treatment of patients. Although limited by the lack of large randomized clinical trials, a metaanalysis of retrospective data has indicated that such patients are also at substantial risk of death, which can be effectively reduced by successful revascularization. Furthermore, pre-operative assessment of viability may identify patients who are at low risk of serious perioperative complications. The prognostic significance of myocardial scars detected by delayed enhancement is currently under investigation. Among 159 patients with clinical suspicion of CAD but without a history of myocardial infarction, the presence of even small amounts of delayed enhancement was associated with a high risk of major adverse clinical events (hazard ratio 8.29 for death, acute myocardial infarction or unstable angina pectoris, hospitalization for heart failure, and life-threatening arrhythmias requiring defibrillation) and cardiac death (hazard ratio 10.9) during a follow-up period of 16 months [50].
It is important to emphasize that delayed-enhancement MRI is specific for either acute myocardial infarction or scar of old infarction, but not for hibernating myocardium. Plain infarct size carries well-established prognostic value that is also expected to apply to MRI. However, in contrast, the prognostic value of PET relies on the relative comparison of flow and glucose uptake (mismatch), which has been shown experimentally and clinically to reflect viable, but jeopardized myocardium. Several studies have indicated that there is an association between PET "mismatch" and adverse clinical outcome [3]. There is a need for prospective clinical trials comparing measures of infarction and either hibernation or stunning obtained with MRI and PET to obtain prognostic data to better understand whether they provide complementary clinical value.

Our research team has high level of expertise in advanced cardiac MRI and cardiac PET imaging techniques and clinical applications. Dr Ordovas has multiple prior publications on viability and functional imaging and its applications in ischemic and non-ischemic heart disease. She has a previous work on border zone response to chronic vasodilator therapy. Dr Pampaloni has studied and published cardiac PET applications for perfusion and viability, with special focus on quantitative imaging.
Dr Saloner has extensive experience with cardiac MR techniques for myocardial strain imaging, and multiple publications on the topic.
Dr Michael Hope has previous publications on aortic imaging and 4d flow MR techniques for flow characterization of patients with bicuspid aortic valve.

10.3 References:

References

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If you have a separate bibliography, attach it to the submission with your other study documents.

11.0 Sample Size and Eligibility

11.1 Number of subjects that will be enrolled at UCSF and affiliated institutions:

60

11.2 Total number of subjects that will be enrolled at all sites (Help Text updated 9/13):

60

11.3 Estimated number of people that you will need to consent and screen here (but not necessarily enroll) to get the needed subjects:

120

11.4 Explain how and why the number of subjects was chosen (Help Text updated 9/13):

This is a pilot study and we anticipate a number of 50 patients to obtain data to generate a formal sample size calculation for a larger trial.

11.5 * Eligible age range(s):

- [ ] 0-6 years
- [ ] 7-12 years
- [ ] 13-17 years
- [x] 18+ years

11.6 Inclusion criteria:

Subjects with ischemic and non-ischemic cardiac disease referred for cardiac PET for viability imaging.

11.7 Exclusion criteria:

Contraindications for MRI, including cardiac pacemaker, claustrophobia, retained metallic foreign body, cochlear implant, Aneurysm clip in the brain, pregnancy and eGFR less than 45%.

11.8 There are inclusion or exclusion criteria based on gender, race or ethnicity:

○ Yes ◉ No

If **yes**, please explain the nature and rationale for the restrictions:

12.0 Drugs and Devices

12.1 * Investigational drugs or biologics will be used OR approved drugs or biologics will be studied under this application:

◉ Yes ○ No

12.2 * Investigational medical devices or in vitro diagnostics will be used OR approved medical devices or in vitro diagnostics will be studied under this application:

◉ Yes ○ No

12.3 * A Non-Significant Risk (NSR) determination is being requested for an investigational device:

◉ Yes ○ No

12.4 Verification of IND/IDE numbers: If the sponsor's protocol does not list the IND/IDE number, you must submit documentation from the sponsor or FDA identifying the IND/IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet.

13.0 Study Drug Details

13.1 List the drugs or biologics that will be studied:

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
	Trade Drug Name: Gadavist **Generic Drug Name:** Gadobutrol **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	Gadavist
Generic Drug Name:	Gadobutrol

Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	This drug is currently used in MRI exams.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug /biologic:	

14.0 Study Device Details

14.1 List the medical devices or in vitro diagnostics to be studied or used and attach any FDA or sponsor correspondence relating to the device to the application in the Study Documents section: (Note: Device category descriptions added to the Help link December, 2014)

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	GE PET/MRI	No	Yes	

Manufacturer/Supplier of Device	
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	No
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A

IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

15.0 Non-Significant Risk Determination for an Investigational Device

15.1 Explain why the use of the device in this study poses non-significant risk:

The PET/MRI study device is classified as non-significant risk in accordance with the definition of a significant risk device provided in 21 CFR Part 812.3(m):
It is not intended as an implant; 2) is not purported or represented to be for a use in supporting or sustaining human life; 3) is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; 4) and it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject (refer to additional study controls below).
Additional study controls:

For parameters besides Specific Absorption Rate (SAR), the study will comply with the non-significant risk limits described in the guidance 'Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices', dated July 14, 2003. For SAR parameters, the device within the study will be tested and required to comply with the risk limits identified in IEC 60601-2-33 Ed. 3.0 Medical electrical equipment – Part 2-33: Particular requirements for the basic safety and essential performance of magnetic resonance equipment for medical diagnosis, which is a FDA Recognized Consensus standard.

Attach any supporting documentation (e.g. any reports of prior investigations) at the end of the application.

16.0 Other Approvals and Registrations

16.1 * Do any study activities take place on patient care units:

○ Yes ◉ No

If **Yes**, attach a letter of support for the study from the involved patient care manager(s).

16.2 * Does your protocol involve any radiation exposure to patients/subjects? The UCSF Radiation Safety Committee requires review of your protocol if it includes administration of radiation as part of standard of care OR research exposures:

○ Yes ◉ No

16.3 * This study may generate genetic data that may be broadly shared (e.g. submitted to NIH for Genome-Wide Association Studies (GWAS) in dbGaP, TCGA, etc):

○ Yes ◉ No

16.4 * This study involves administration of vaccines produced using recombinant DNA technologies to human subjects:

○ Yes ◉ No

16.5 * This study involves human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory

Committee (RAC) review prior to CHR approval):

○ Yes ◉ No

16.6 This study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☑ Radiation Safety Committee

Specify RUA #:

☐ Radioactive Drug Research Committee (RDRC)

Specify RDRC #:

☐ Controlled Substances

17.0 Procedures

17.1 * Procedures/Methods (Help Text updated 9/13) For clinical research list all study procedures, test and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the Methods:

The subjects will undergo PET/MR for study purposes after they have finished their clinically indicated PET/CT, with no additional venipuncture to the patients.

We propose to use 5D MR imaging (3D in space, in time through the cardiac cycle, and in time through the respiratory cycle) to provide improved information on the location of the signal source during PET acquisition.

Dynamic and static PET data will be acquired in list mode and retrospectively rebinned according to predicted location from MR data.

Accelerated MR methods (including compressed sensing) will be used to give rapid assessment of volumes over time.

Additional MR imaging sequences will include strain mapping and VEC-MRI for flow imaging. In addition gadolium delayed enhancement will be obtained for myocardial tissue characterization with MRI.

If you have a procedure table, attach it to the submission with your other study documents.

17.2 Interviews, questionnaires, and/or surveys will be administered or focus groups will be conducted:

○ Yes ◉ No

List any standard instruments used for this study:

Attach any non-standard instruments at the end of the application.

17.3 Conduct of study procedures or tests off-site by non-UCSF personnel:

○ Yes ◉ No

If yes, explain:

17.4 Sharing of experimental research test results with subjects or their care providers:

○ Yes ◉ No

If yes, explain:

17.5 * Specimen collection for future research and/or specimen repository/bank administration:

○ Yes ◉ No

17.6 Time commitment (per visit and in total):

1 hour in the scanner.

17.7 Locations:

The cardiac MRI will take place at the China Basin radiology.

17.8 Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants:

1. The research team will make several efforts to keep the PHI under extreme security, including the use of a coded database, password protected computers and locked cabinets, which will all be kept inside a locked office at the Parnassus campus.
2. Patients are screened for prior claustrophobic symptoms using a screening form. Earplugs are provided to all patients in order to minimize the discomfort related to the loud noise.
3. Loose metal objects are not allowed in the MR room. All entrances to the scanners are clearly marked with signs warning people not to enter with any metal and by each entrance there is a mobile metal detector.
4. All patients fill up a screening form for any incompatible devices and metallic foreign bodies prior to entering the MR scanner room.

18.0 Alternatives

18.1 Study drug or treatment is available off-study:

○ Yes

○ No

◉ Not applicable

18.2 * Is there a standard of care (SOC) or usual care that would be offered to prospective subjects at UCSF (or the study site) if they did not participate:

◉ Yes ○ No

If yes, describe the SOC or usual care that patients would receive if they choose not to participate:

If patients do not participate on the study, they will still receive the standard FDG PET-CT per clinical request.

18.3 Describe other alternatives to study participation that are available to prospective subjects:

Not to participate.

19.0 Risks and Benefits

19.1 * Risks and discomforts:

The main risks to subjects for participating in this study are related to breach of confidentiality and exposure to the MRI scanner.
No significant physical, psychological, financial, or legal harm is anticipated in case subject's confidentiality is inadvertently breached.
Risks associated with the MRI study are stratified based on probability of occurrence and listed below:
Common:
MR imaging may cause some discomfort, such as feelings of claustrophobia and discomfort due to loud sounds of the MR instrument during the study.
Uncommon/Rare:
Another potential hazard of the exam is localized heating of the body due to the radio waves employed. MR scanner and the MR probes have been designed to reduce the chance of heating.
Because the MR scanner attracts iron, there is a small possibility that an iron-containing object could accidentally fly into the magnet causing injury to the patient.
The presence of some metallic implantable devices or foreign bodies represents formal contra-indication to MR imaging and exposure to the strong magnetic field may cause malfunction or dislodgement of such devices or foreign bodies, potentially harming patients. A cardiac pacemaker is one example.
Gadolinium is considered to be very safe for most people. Side effects from gadolinium itself are very rare. These side effects are usually headache and nausea. There have been a very few people who have had allergic reactions to gadolinium. Most people with allergic reactions get hives. Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life threatening. There are no reports of NSF in patients with normal kidney function.

19.2 Steps taken to minimize risks to subjects:

1) The research team will make several efforts to keep the PHI under extreme security, including the use of a coded database, password protected computers and locked cabinets, which will all be kept inside a locked office at the Parnassus campus.
2) Patients are screened for prior claustrophobic symptoms using a screening form. Earplugs are provided to all patients in order to minimize the discomfort related to the loud noise.
3) Loose metal objects are not allowed in the MR room. All entrances to the scanners are clearly marked with signs warning people not to enter with any metal and by each entrance there is a mobile metal detector.
4) All patients fill up a screening form for any incompatible devices and metallic foreign bodies prior to entering the MR scanner room.
5) Gadolinium: There have been a very few people who have had allergic reactions to gadolinium. Most people with allergic reactions get hives. These are usually very mild and require no treatment. Sometimes people will receive Benadryl to help relieve any itching. Subjects may experience a temporary discomfort from the needle stick, bruising, and rarely infection. Before the subject undergo an MRI requiring an

injection of gadolinium contrast, we will review his medical record for results of a blood test to check the renal function. If the subject have not had a recent laboratory test done for that purpose, we will obtain that blood test on the day of the study, without the need for an additional puncture. Based on his medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI.

19.3 Benefits to subjects:

○ Yes ◉ No

If yes, describe:

No direct benefit for the patients; however, future patients could benefit from the combined acquisition of PET/MRI for management of their cardiac disease.

19.4 Benefits to society:

The combined acquisition of PET/MRI may be a reliable diagnostic and prognostic tool for patients with cardiac disease.

19.5 Explain why the risks to subjects are reasonable:

MR imaging may cause some discomfort, such as feelings of claustrophobia and discomfort due to loud sounds of the MR instrument during the study. These discomfort and risks will be outweighed by the possibility of a reliable diagnostic and prognostic tool for patients with cardiac disease.

20.0 Data and Safety Monitoring Plan

20.1 Describe the plan for monitoring data and safety (Help Text updated 9/13):

One of the study investigators will be present during the study acquisition and will document any possible adverse reaction on a log book. Dr Ordovas and Dr Pampaloni will review the log book to confirm absence of adverse events once a week. In case of a minor adverse event, CHR will be informed within one week. In the unlikely event of a significant adverse event, CHR will be informed within 24 hours.

20.2 This study requires a Data and Safety Monitoring Board:

○ Yes
◉ No or not sure

If **yes**, press **SAVE and CONTINUE** to move to the next section of the application.

20.3 If No, provide rationale:

○ Social/Behavioral research
○ Phase I trial
○ Treatment IND/Compassionate Use Trial
◉ Other (explain below)

If **Other,** explain:

It does not make criteria for the Data and Safety Monitoring Board.

21.0 Confidentiality and Privacy

21.1 Plans for maintaining privacy in the research setting:

The research team will make several efforts to keep the PHI under extreme security, including the use of a coded database, password protected computers and locked cabinets, which will all be kept inside a locked office at the Parnassus campus.

21.2 Possible consequences to subjects resulting from a loss of privacy:

No significant physical, psychological, financial, or legal harm is anticipated in case subject's confidentiality is inadvertently breached.

21.3 Study data are:

- [ ] Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
- [x] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [ ] Added to the hospital or clinical medical record
- [ ] Created or collected as part of health care
- [ ] Used to make health care decisions
- [ ] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained from a foreign country or countries only
- [ ] Obtained from records open to the public
- [ ] Obtained from existing research records
- [ ] None of the above

If **derived from a medical record**, identify source:

21.4 Identifiers may be included in research records:

- (•) Yes
- ( ) No

If **yes**, check all the identifiers that may be included:

- [x] Names
- [x] Dates
- [ ] Postal addresses
- [ ] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers

- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier

* Required for studies conducted at the VAMC

21.5 Identifiable information might be disclosed as part of study activities:

- (•) Yes ( ) No

If **yes**, indicate to whom identifiable information may be disclosed:

- [ ] The subject's medical record
- [x] The study sponsor
- [ ] Collaborators
- [x] The US Food & Drug Administration (FDA)
- [ ] Others (specify below)
- [ ] A Foreign Country or Countries (specify below)

If **Others**, specify:

21.6 Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- [ ] Data are stored securely in My Research
- [x] Data are coded; data key is destroyed at end of study
- [x] Data are coded; data key is kept separately and securely
- [x] Data are kept in a locked file cabinet
- [x] Data are kept in a locked office or suite
- [x] Electronic data are protected with a password
- [ ] Data are stored on a secure network
- [ ] Data are collected/stored using REDCap or REDCap Survey
- [ ] Data are securely stored in OnCore

21.7 Additional measures to assure confidentiality and protect identifiers from improper use and disclosure, if any:

21.8 This study may collect information that State or Federal law requires to be reported to other officials or ethically requires action:

- ( ) Yes (•) No

Explain:

21.9 This study will be issued a Certificate of Confidentiality:

- ( ) Yes (•) No

22.0 Subjects

22.1 Check all types of subjects that may be enrolled:

- [x] Inpatients
- [x] Outpatients
- [ ] Healthy volunteers
- [ ] Staff of UCSF or affiliated institutions

22.2 Additional vulnerable populations:

- [ ] Children
- [ ] Subjects unable to consent for themselves
- [ ] Subjects unable to consent for themselves (emergency setting)
- [ ] Subjects with diminished capacity to consent
- [ ] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners
- [ ] Economically or educationally disadvantaged persons
- [ ] Investigators' staff
- [ ] Students

Explain why it is appropriate to include the types of subjects checked above in this particular study:

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

23.0 Recruitment

23.1 * Methods (check all that apply):

- [x] Study investigators (and/or affiliated nurses or staff) recruit their own patients directly in person or by phone.
- [ ] Study investigators recruit their own patients by letter. Attach the letter for review.
- [ ] Study investigators send a "Dear Doctor" letter to colleagues asking for referrals of eligible patients. If interested, the patient will contact the PI or the PI may directly recruit the patients (with documented permission from the patient). Investigators may give the referring physicians a study information sheet for the patients.
- [ ] Study investigators provide their colleagues with a "Dear Patient" letter describing the study. This letter can be signed by the treating physicians and would inform the patients how to contact the study investigators. The study investigators may not have access to patient names and addresses for mailing
- [ ] Advertisements, notices, and/or media used to recruit subjects. Interested subjects initiate contact with study investigators. Attach ads, notices, or media text for review. In section below, please explain where ads will be posted.
- [ ] Study investigators identify prospective subjects through chart review. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [ ] Large-scale epidemiological studies and/or population-based studies: Prospective subjects are identified through a registry or medical records and contacted by someone other than their personal physician. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [ ] Direct contact of potential subjects who have previously given consent to be contacted for participation in research. Clinic or program develops a CHR-approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form for another CHR-approved study.
- [ ] Study investigators list the study on the School of Medicine list of UCSF Clinical Trials website or a similarly managed site. Interested subjects initiate contact with investigators.

☐ Study investigators recruit potential subjects who are unknown to them through methods such as snowball sampling, direct approach, use of social networks, and random digit dialing.

☑ Other

If **Other**, explain:

Inpatients and outpatients referred for clinically indicated FGD-PET are going to be invited for participation in this study. The investigators will explain in detail the study and will provide the informed consent to the potential subject. The investigators will clarify any doubts related to the informed consent and/or the study.

23.2 * How, when, and by whom eligibility will be determined:

The patients will be approached (by phone call) by one of the investigators before they arrive at the Radiology department for the clinically indicated FGD-PET.

23.3 * How, when, where and by whom potential subjects will be approached:

The investigator will look for exclusion criteria of scheduled patients for FGD-PET . The patients will be approached by phone call before their scheduled appointment at the Radiology department for the clinically indicated FGD-PET.

23.4 * Protected health information (PHI) will be accessed prior to obtaining consent:

◉ Yes ○ No

24.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when study investigators (and/or affiliated nurses or staff) recruit their own patients directly.

24.1 * Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified:

◉ Yes

If **no**, a waiver of consent/authorization is NOT needed.

24.2 * A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

◉ Yes

If **no**, a waiver of authorization can NOT be granted.

24.3 * Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

◉ Yes

If **no**, a waiver of authorization can NOT be granted.

24.4 * Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [ ] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

24.5 * Describe any health information that will be collected prior to obtaining informed consent:

Name, phone number and presence of contraindications (history of cardiac pacemaker, retained metallic foreign body, cochlear implant, aneurysm clip in the brain, claustrophobia, pregnancy and eGFR less than 45%) to the MR exam.

Note: HIPAA requires that you collect the minimum necessary.

24.6 * Describe your plan to destroy the identifiers at the earliest opportunity consistent with the research or provide a health or research justification for retaining the identifiers, or indicate and explain that retention is required by law:

As soon as this study is finished, all the data will be destroyed, physically and virtually.

25.0 Informed Consent

25.1 * Methods (check all that apply):

- [x] Signed consent will be obtained from subjects and/or parents (if subjects are minors)
- [ ] Verbal consent will be obtained from subjects using an information sheet or script
- [ ] Electronic consent will be obtained from subjects via the web or email
- [ ] Implied consent will be obtained via mail, the web or email
- [ ] Signed consent will be obtained from surrogates
- [ ] Emergency waiver of consent is being requested for subjects unable to provide consent
- [ ] Informed consent will not be obtained

25.2 * Process for obtaining informed consent:

An investigator will invite potential patients that were referred for clinically indicated FGD-PET for study participation before their exam.

25.3 * How investigators will make sure subjects understand the information provided to them:

Investigators will talk in a lay language and will be available to clarify any doubts regarding any questions.

26.0 Financial Considerations

26.1 Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [x] Subjects will not be paid
- [ ] Cash
- [ ] Check
- [ ] Debit card
- [ ] Gift card
- [ ] Reimbursement for parking and other expenses
- [ ] Other:

Specify **Other**:

26.2 Describe the schedule and amounts of payments, including the total subjects can receive for completing the study. If deviating from recommendations in Subject Payment Guidelines, include specific justification below.

Subjects will not be paid.

26.3 Costs to Subjects: Will subjects or their insurance be charged for any study procedures?

( ) Yes (•) No

If **yes,** describe those costs below, and compare subjects' costs to the costs associated with alternative care off-study. Finally, explain why it is appropriate to charge those costs to the subjects.

27.0 CTSI Screening Questions

27.1 * This study will be carried out at one of the UCSF Clinical Research Services (CRS) centers or will utilize CRS services. CRS centers are at the following sites:

- **SFGH Clinical Research Center**
- **Moffitt Adult Clinical Research Center**
- **Moffitt Hospital Pediatrics & NCRC**
- **Mount Zion Hospital Clinical Research Center**
- **Tenderloin Center**
- **CHORI Children's Hospital Pediatrics & Adult Clinical Research Center**
- **Kaiser Oakland Research Unit**
- **SF VA Medical Center Clinical Research Unit**

Please note: Effective 3/1/14, the CRS form will no longer be completed and submitted in iRIS. The CRS budget request form can be found at: https://accelerate.ucsf.edu/files/crs/BudgetRequest2015.docx. Follow the instructions on the form to submit. Even if you click 'Yes' to this question, the form will no longer proceed to the Clinical Research Services (CRS) Application Form section.

○ Yes ◉ No

27.2 This project involves community-based research:

○ Yes ◉ No

27.3 This project involves practice-based research:

○ Yes ◉ No

28.0 End of Study Application

28.1 End of Study Application Form

To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.