SOP 04: P-MRI MRI Procedure and Image(s) Storage

1.0 Overview

This document describes the standard operating procedures for transfer of DICOM imaging files via Aspera to the Jet Propulsion Laboratory (JPL) for the EDRN Prostate MRI Study (P-MRI). These data include magnetic resonance imaging (MRI). The scope of this SOP only pertains to the transfer of data procedures and security of data defined herein. Changes to this document must be confirmed and approved by the Imaging Core. Version control is handled by the Data Management and Coordinating Center (DMCC). Extracted data from Radiology Reports is key-entered into the Validation Study Information Management System (VSIMS) and stored into the DMCC database. The link between the DICOM Images at JPL and the Clinical Data in VSIMS is managed by an Image Event Identifier with the DMCC holding the link.

1.1 Study Initiation

Primary information about the institutions current MRI-Ultrasound Fusion biopsy workflow and personnel will be obtained using a pre-study EDRN MRI initiation questionnaire. This will provide EDRN Lead investigators the ability to assist new sites in set up and anticipate logistical issues. Once the site is preliminarily approved; the site PI urologist and radiologist are assigned. On boarding and vetting will take place by study team members (Matt Davenport, Mike Liss and Radka Stoyanova, aka Imaging Core)

1.2 Qualifications for study radiologist

The study will conduct a survey of individual radiologists who are nominated to be study radiologists to collect data on imaging and their experience. Given that there may be a range of experience with regards to reading prostate MRI, minimal requirements and/or training will be necessary. All study radiologists must at minimum have 1 year experience interpreting body MRI. If a radiologist has read over 100 prostate MRI combined with fusion prostate biopsy using PIRADS v.2 standard, then that is sufficient. All other radiologists will undergo a vetting process to ensure adequate accuracy and inter-rater reliability. The process will include interpretation of 20 prostate MRI exams with a range of PIRADS v2 scores. Minimum pairwise intraclass correlation between the site radiologist and the study team radiologist will be 0.5. If not achieved, sets of 10 additional studies will be reviewed until the target ICC is achieved. As part of ongoing quality assurance, 10% of MRI examinations will undergo a secondary review at least twice per year to identify outlier institutions that may benefit from additional training in MRI interpretation (radiologist) and biopsy outcomes (urologist).

1.3 MRI Acquisition and Specifications

PIRADS V.2 protocol is the standard for all EDRN MRIs. Each site will submit their current imaging protocol for review. The MRI Team can determine if the sequences meet PIRADS v2 parameters. PIRADS v2 recommends:

- TE: ≤ 90 msec; TR : ≥ 3000 msec
- Slice thickness: ≤4mm, no gap.
- Field of view (FOV): 16 - 22 cm
- In plane dimension: ≤2.5mm phase and frequency

DCE MRI is defined as the acquisition of rapid T1W gradient echo scans before, during and after the intravenous administration of gadolinium.

In order to generate reliable ADC maps, we are recommending at least 3 b-values with at least one being in the high-b-value range (>1400 sec/mm2), and others within the ranges as described:

B Value 0
B Value 50 - 100 sec/mm^2
B Value 400 - 600 sec/mm^2
B Value 800 - 1000 sec/mm^2
B Value 1400 - 1600 sec/mm^2

1.4 MRI Calibration and Quality Control

MRI Phantom (4 sites minimum)

We will evaluate study site imaging variability and provide related recommendations to obtain compliance and improve generalizability. The table below shows acceptable scanner parameter settings. A commercial diffusion phantom (High

Precision Devices, HPD or similar provider) that will be capable of containing different fluids will be used for the study. We will modify the phantom by doping available insert tubes with different concentrations of GdCl2 (up to six, with 0.0, 0.125, 0.25, 0.50, 1.0 and 3.0 mM), which will assist in qualifying the contrast enhancement. Image data sets will be used to develop quantitative analytical metrics to assess scanner accuracy, precision, and reproducibility.

1. Image data sets will be used to develop quantitative analytical metrics to assess scanner accuracy, precision, and reproducibility.
    - **a.** We will use T2 weighted images to segment the various ROIs and tag them.
    - **b.** For T1 and T1-weighted images we will calculate:
        1. The linearity across T1 values and increasing concentrations of Gd to represent a time-activity-curve (TAC).
        2. The intra-session reproducibility across all acquisitions (about 30) for each of the Gd-containing samples, as well as the slope.
    - **c.** For ADC, we will use the open source software QIBAphan developed by T. Chenevert as part of the QIBA effort and/or develop a processing workflow at Moffitt Cancer Center (using commercial PACS imaging suites):
        1. We will first determine how many scans of each acquisition to combine to achieve comparable SNR at each b-value. These combined scans will then be used in subsequent analyses.
        2. We will determine the log-linearity of the QIBA standard 0-500-900 series, compared to the clinical standards of 50-500-1000 series by fitting to Steskja-Tanner.
        3. We will compare ADC values obtained from each series to published values for the phantom.
        4. We will determine the inter-session stability of the ADC measured with each series.

2. ***Statistical plan***: We will compute area under the "time activity curve" (AUC for TAC) for each scanner setting and repeats. After data standardization (with respect to initial intensity levels), we will compute coefficient of variation (CV) on the repeats for a setting, repeated for different parameters and repeated across the groups. We will also compute repeatability coefficient (RC) for each groups repeats.

   We plan to compute Concordance correlation coefficient (CCC) between different institutional scanner image regions estimates (mean, median, deviation on ADC, DWI regions, AUC for TAC) for a given scanner setting (B-value/scanner parameter).

3. **Evaluation score**: (a) Computed Coefficient of Variation (CV) for multiple repeats at a scanner setting will evaluate repeatability of the measurement. We will provide confidence levels for these estimates (95%). RC metric will additionally provide bounds for the variability within the participating center (b) We will evaluate reproducibility of measurement by computing concordance correlation in ADC, DWI (b-value regions), AUC of TAC between scanners, across institutions for different settings (*Expected concordance between teams: 80% or above).*

   Scanner parameters will be selected based on highest Concordance across -institutions with high level of repeatability (CV expected to be 5% with in centers and 10% between centers with a mean variability of 10% for both situations). Each center will obtain 4 scans for each setting to validate repeatability (with-in centers) and 15 repeats to validate between centers (between-centers) reproducibility.

4. ***Scanner Grading:*** We will grade scanners using both evaluation metrics. Scanners should provide reproducible measurements based in CV (5% with-in centers) and RC coefficient. Data should have high concordance with the other teams, CV with-in 10% and high CCC (85% or greater). For each site, we will also compute metrics differences between the standard protocol and the preferred site-specific prostate protocol. These data will be

used to determine the magnitude of site-specific protocol deviations, and whether the can be corrected with post-processing.

5. **Sample Size:** We expect the observed CVs to be around 5% (with-in centers) and a CV about 15% for between centers, anything above would be unacceptable and will be flagged. The centers would be requested to look for causes for the variability. In this study, a sample size of 4 sample repeats would be needed to achieve 80% power to detect a mean difference of 10% for with-in each centers imaging repeats, assuming a two-sided test with 5% false positive rate.

   The inter-institutional variability for coefficient of variation is expected to be 10% between centers with a mean variability of 10%, which would need 15 repeats per centers (for a mean variability of 15%, the sample size will reduce to 7) to observe the variability. The study assumes a power of 80% and a false positive rate of 5%. While the study power calculation is based on our primary measure, CV. In the analysis we will also consider concordance correlation coefficients (CCC) as an alternative measure for image quality. This is particularly useful in concordance of continuous measures without making the linear assumptions as used in Spearman correlation.

   Based on above sample size computations, each participating center will be expected to run about 15 repeats for a setting to quantify intra-institutional and inter-institutional variability measure.

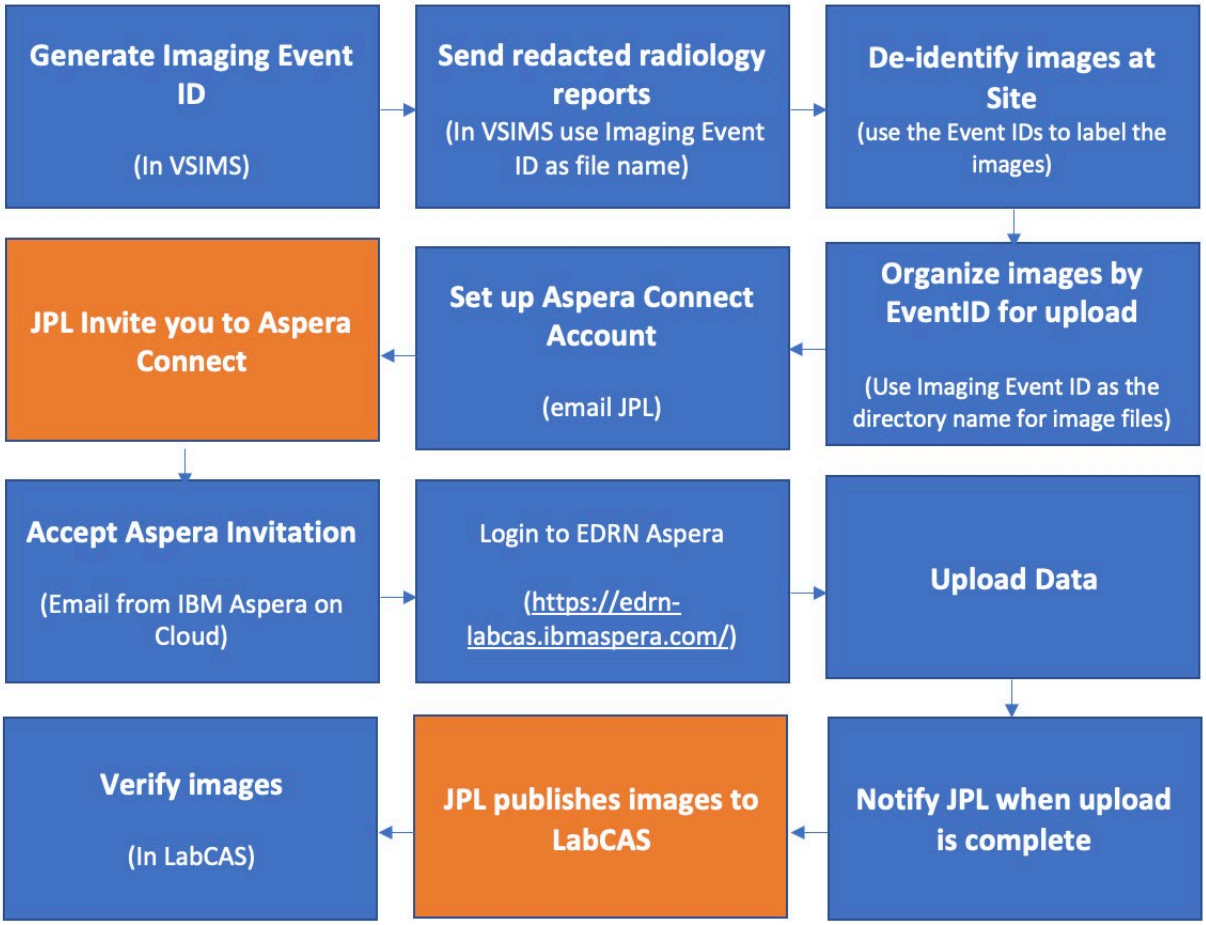
Table 1:

MRI Acquisition Parameters for Phantom. (Ranges of values represent the full ranges that are used clinically)					
	T2-Weighted*	**T1-Weighted****	**DWI†**	**T2 large FOV (optional)**	
Sequence	TSE (etl 28) SE	GE GR	EPI EP/SE	SE	
TR (ms)	5570 3800	4.87 3.06	6000 9500	10723	
TE (ms)	109 87.12	1.88 1.372	90 52.5	82.104	
Flip Angle (degrees)	140 111	12 12	90 90		
Voxel Size(mm)	0.36 x 0.36 x 3.0 0.391x0.391x3.5	1.35 x 1.35 x 3.5 1.02x1.02x2.5	1.27 x 1.27 x 3 1.25x1.25x2.5	1.25x1.25x2.5	
Image Size	640 x 640 512x512x27	192 x 192 256x256x36	170 x 172 256x256x36	256x256x72	
DWI b-values			150 – 900 – 1000 - 1500 50-500-1000 - 1400 Could be adjusted if necessary		
Summary Comments/ Foot notes	*The first three sequences (shaded in yellow) are according to the Dynacad protocol. Three sets of T2-weighted MRI in axial, sagittal and coronal orientation are acquired. † DWI in four directions is measured by using B-values – 50, 500, 1000 s/mm^2				

1.5 Image Transfer and Repository

Study sites will transfer **de-identified** data to NASA Jet Propulsion Laboratory (JPL) for archiving in DICOM format. Prior to transferring data to JPL an anonymized Image **Event ID** must be generated in VSIMS and used as the MRI directory name to label the MRI data (see example below). **Redacted radiology reports with the file named as the Event Identifier need to be upload through the Data Transfer Feature in VSIMS**. The Imaging Event ID will be generated automatically in VSIMS upon first submission of either the P-MRI MRI form (Form ID 2508) or the P-MRI MRI Follow-up form (Form ID 2519). The Image Event ID generated will be shared with whoever, at each site, is de-identifying and naming the imaging files for use in this study. Data will be deposited into the LabCAS ("Laboratory Catalog and Archive Services"), a web-enabled environment that allows users to publish, share, search and download a wide variety of biomedical datasets. In LabCAS, data is organized according to the following logical hierarchy: Collections: broad sets of related data from the same study, the same analysis, or the same project; Datasets: different sets of related files within the same collection; and Files: all the files in a given dataset. Metadata will be associated with the data that will include identifiers to ensure a link to the clinical data stored in VSIMS. Sites will use Aspera Connect to transfer files to JPL.

The diagram below walks through the entire image upload process. Steps in blue are performed by the site and steps in orange or performed by JPL.



Step 1. Documentation of authorization for data transfer.

Each recruiting site will send proof of IRB approval allowing MRI images to be transferred to JPL to the DMCC. The DMCC will ensure that JPL has IRB approval for warehousing the images. If the recruiting site requires a Data Use Agreement between their institution and JPL, then the recruiting institute is responsible for initiating the DUA. Each recruiting site will determine the following (1) the number of subjects and files to be transferred, (2) the nature of the transfer (prospective/ongoing collection), (3) the process by which data will be de-identified, (4) a technical contact who will facilitate data transfer and (5) a data access policy for de-identified imaging data.

Step 2. Definition of transfer protocol and de-identification method

De-identified images will be sent to JPL via IBM Aspera Connect, a secure, fast and reliable data transfer tool.

Data de-identification: JPL does not store identified imaging data on its imaging servers. The DMCC maintains a link that links imaging identifiers, the Imaging Event ID, with patient identifiers and other common data elements (CDEs) defined by the study. JPL requires that each recruiting site de-identifies all images prior to data transfer to meet their IRB requirements.

Step 3. Transfer, review, and de-identification of data

3.1 Setup Data Transfer

To upload data into LabCAS, you'll use IBM Aspera Connect.:

1. Contact the JPL Informatics Center by email at ic-data@jpl.nasa.gov: Include the following:
    a. Your name and Institution
    b. The email address you would like to use for your IBMid Aspera account.
    c. The project name for which you will be uploading data, such as the "EDRN PMRI"
2. JPL Team will receive your email and send you an invitation to join the Aspera on Cloud instance designated for EDRN.
3. Accept the Invitation: Look out for the email invitation in your inbox, and click the "Accept" button within the message. This action will direct you to the EDRN Aspera login page. Note: The invitation comes via email from IBM servers but may end up in your junk folder. Please check the junk folder if the invitation hasn't arrived within 1-2 business days.

3.2 Upload your data

3.2.1 Confirm Images

Confirm that your data is de-identified and anonymized using the VSIMS Imaging Event ID. For example, if the VSIMS Image Event ID is 1234567, your MRI files associated with that Event would all be under a directory named 1234567.

1234567

Image0001.dcm

Image0002.dcm

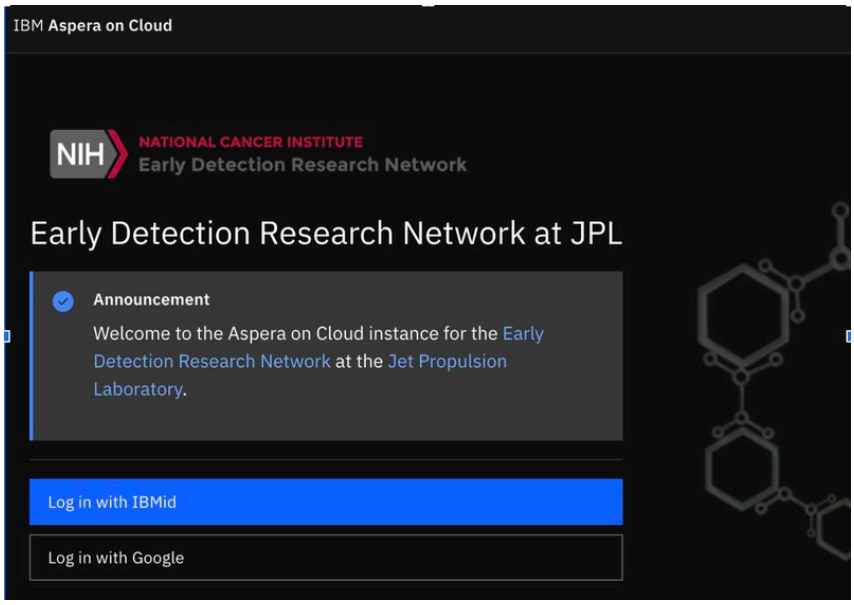
Image0003.dcm

JPL will append each image filename with the Event ID upon publishing to LabCAS to ensure the link is maintained between images and VSIMS data.

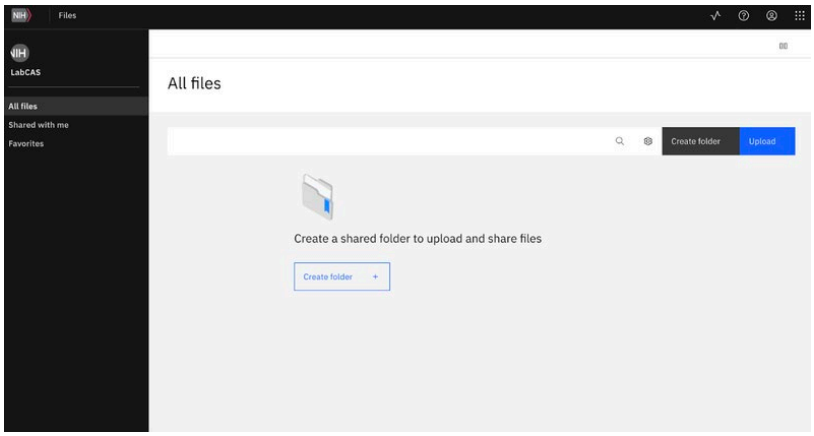
If your DICOM images are on a CD-ROM and have additional files, you can upload the entire CD-ROM as long as the images are in the directory structure above with the Event ID as the directory with the appropriate MRI files under that directory.

3.2.2 Upload Images

Navigate to EDRN Aspera by visiting → https://edrn-labcas.ibmaspera.com/:



1. Sign in using your email address credentials or your IBMid.



2. Navigate to the files on your computer and drag and drop

   OR

   Click the 🔍 to find the files

3. Click Upload

Note: The first time, a small helper application, “Aspera Connect”, may be downloaded and installed.

4. Notify the JPL Informatics Center that your data transfer is complete by emailing ic-data@jpl.nasa.gov
   - Include your VSIMS username so we can provide you with permissions to view your sites images in LabCAS.

Step 4. Publishing and verifying data

Once the data are transferred to JPL, the JPL team will ingest the data into LabCAS with appropriate metadata. JPL will communicate with sites if there are any data transfer errors as soon as pragmatic to ensure efficient and accurate data transfer. After data has been published, they will contact the data submitter for review.

Sites will have access to view their sites images in LabCAS by requesting EDRN Secure Site access at https://www.compass.fhcrc.org/edrns/pub/user/application.aspx?t=app&sub=form1&w=1&p=3

Data submitters will login and review data that is in LabCAS (https://edrn-labcas.jpl.nasa.gov/) and compare it to the data that was intended to be sent. Any and all error(s) that may happen will be reviewed and documented (with special consideration that no identifying data is stored in such documents).

Please note: filenames will have the VSIMS Event ID appended to the name upon publishing to LabCAS.

After quality assurance, the imaging data will be accessible to the appropriate groups within LabCAS. Initially, only the site itself and the DMCC statisticians will have access to the images for analysis. Once the DMCC develops a process with the investigators to ensure blinding, images may be shared upon approval.

1.6 MRI Imaging Reading and Assessment

Images will be evaluated using a five-point scale (PI-RADS version 2) to determine degree of suspicion for clinically significant prostate cancer. Study approved radiologists will determine each PI-RADS v2 score for receiver operating characteristic analysis. If a non-approved radiologist reads the MRI, the MRI will undergo secondary review by the site-approved radiologists and both reads will be stored for later comparison. All study-related biopsies must be directed by interpretations performed by study-approved radiologists. For study purposes, the approved radiologists read will be final.

PI - RADS™ v2 Assessment Categories

PIRADS 1 – Very low (clinically significant cancer is highly unlikely to be present)
PIRADS 2 – Low (clinically significant cancer is unlikely to be present)
PIRADS 3 – Intermediate (the presence of clinically significant cancer is equivocal)
PIRADS 4 – High (clinically significant cancer is likely to be present)
PIRADS 5 – Very high (clinically significant cancer is highly likely to be present)

Region(s) of interest identified by the study team radiologists at each site will be contoured using DynaCAD software if using UroNav by Invivo or corresponding other system. All processed ROI images will need to be saved. All images with post-processing will be uploaded along with the processing summary in the HIPAA compliant archive online for research use and quality assessment (LabCAS). After the MRI, the patient will undergo MRI-Fusion prostate biopsy.

1.7 MRI Fusion Prostate Biopsy

In order to later obtain appropriately labeled samples and images that could be overlaid onto MRI images in order to attain accurate biopsy locations, proper labeling at the time of the biopsy must be consistent.
10.1016/j.juro.2013.02.072

1.8 Data Security

Clinical and Specimen Data

All Clinical Data is stored in VSIMS using a de-identified patient identifier. The DMCC and all servers are physically secured behind a card-key access area. Fred Hutchinson Cancer Research Center (FHCRC) staff with authorized access to the DMCC may enter the physical area. All materials and data are stored inside locked offices and server rooms. All DMCC servers are secured in a locked area with extremely limited key distribution. All servers require username and password logins and file permissions are granted on an as needed basis. All DMCC computers have a mandatory screensaver password that is unique for each user.

VSIMS has three levels of security. The first level is a login system that requires a username and password. The second level is the assignment of protocol access to a specified user. For example, if a user is authorized to access a single specified protocol, but VSIMS is managing data for three protocols at that time, the user is only allowed to access that single specified protocol. The third level is the assigned user rights as described in detail below. These user rights are assigned by protocol.

Access to VSIMS requires a username and password distributed and maintained by the DMCC. The username and password are the keys to accessing VSIMS. Everyone who accesses VSIMS should keep this information as safe as the keys to the house or car. Keeping the username and password safe will protect the files in the user's pages of interest and will help guard against unauthorized use. If unscrupulous computer trespassers obtain the username or password, they can use the user's identity as a "home base" to break into the entire web site and database.

To obtain VSIMS access, one must complete an on-line VSIMS Access Application. The applicant must electronically indicate commitment to confidentiality and completion of human subjects training offered within the electronic application form. The DMCC Project Director (or assigned designee) must approve, via email, the applicant for access to VSIMS and assign user rights. (this process is documented in MOP-Appendix 1).

Once the application is processed at the DMCC, the applicant is sent a link, verification code and username via e-mail by which to create a password for future login to the website. The user has three days in which to use the link and validation code to login and change their password. If a user does not use the link and validation code before they expire, they must re-apply.

The DMCC requires the password to be changed every six months. In addition, a user can change his/her password at any time. For security reasons, passwords for the VSIMS secure web site must be at least 8 characters long. If the user's session remains idle for 2 hours, they will be timed out and must log into the system again. Passwords or log-in information may not be shared. If a person attempts to log-in and his/her password has expired, the user is prompted to change his/her password at that time.

Acceptance of the Confidentiality Pledge and completion of the VSIMS Access Application is tracked by a database at the DMCC. A report can be generated at any time to show the VSIMS secure site users.

For security purposes, accounts that are not used for six months are deactivated and accounts that are not used for one year are deleted. Deactivation of an account will require the user to call the DMCC to reactivate it. If a user of a deleted account wants to regain access to the secure web site, he/she must complete a new Access Application. Once a year the DMCC will send an email to the Project Coordinator of each site with a list of people from his/her site who have access to the VSIMS secure site to confirm whether or not all those listed should still have access.

In addition to a username and password, to access VSIMS the user must be using a browser, which supports at least 128-bit strong data encryption. 128-bit strong encryption is recognized as the de facto standard for the secure exchange of information and is the highest internationally available level of encryption used for the exchange of data over the public Internet. Once a connection is made to the site, all communications between the user's browser and the web site are then encrypted. Further security is provided by the use of an authentication certificate provided by a major commercial Certificate Authority such as Thawte, and the DMCC's institutional firewall which blocks access to TCP/IP services not needed for accessing the secure site. The DMCC will continue to monitor the technology and policy changes that allow for continued privacy in data sharing to best serve the needs of EDRN. The DMCC must be notified immediately if a staff member that has VSIMS access no longer works on an assigned protocol so that their account can be disabled.

Imaging Data

De-identified imaging data will be loaded into LabCAS. Access will be controlled via a secure web login. Users may access the data via https://edrn-labcas.jpl.nasa.gov/
upon approval. LabCAS provides a comprehensive security infrastructure including both authentication and authorization. Security services are managed using the Lightweight Directory Access Protocol (LDAP). LDAP manages both users and groups support both authentication of users and mapping of users to groups. Data is annotated into this scheme using a multi-level security architecture. This enables data to be mapped to users who have different roles including data producers, data stewards, and data users whose privileges will be granted and enforced by the system. The data producers can identify which data users can access the data. Data stewards can support annotation and capture of the data. This allows data to be shared with a different investigator or set of investigators. Data stewards can work with the data coordinating center to help appropriately annotate the data for these scenarios. Data is transferred to LabCAS using full 128-bit encryption.

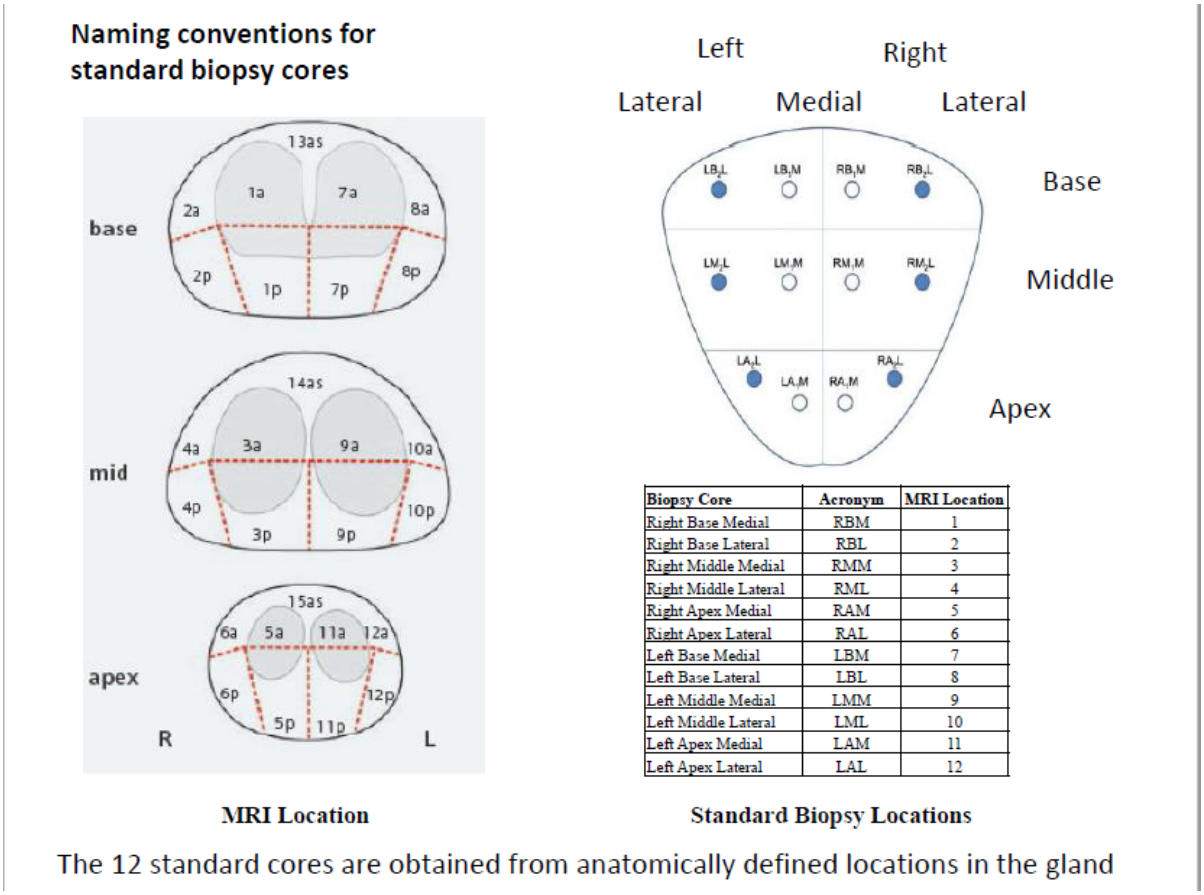
Imaging Data Server Security

Amazon Web Services (AWS) secure cloud platform will be used for the storage of images. AWS and JPL work on a shared responsibility where AWS manages the security of the cloud and JPL manages the security in the cloud. The practical application of this model is that AWS maintains underlying hardware, physical security, and Amazon tool interface security (https://aws.amazon.com/compliance/data-center/controls/) while JPL maintains the security of the virtual network and systems used by the project. In addition, JPL has certified that AWS' security controls meets the JPL security requirements Each virtual system in the cloud fall under a JPL security plan and meet all JPL security requirements such as regular patching, authentication restrictions, network restrictions, and logging. EDRN's AWS instances are included in the JPL IT Security Database (ITSDB) plan 220 which is certified yearly as part of JPL's C&A process.

1.9 Image Dataset Naming Convention

The VSIMS generated Imaging Event ID, as discussed previously in section *Image Transfer and Repository* will be used to label MRI datasets prior to transferring to the JPL image repository.

Figure 1:

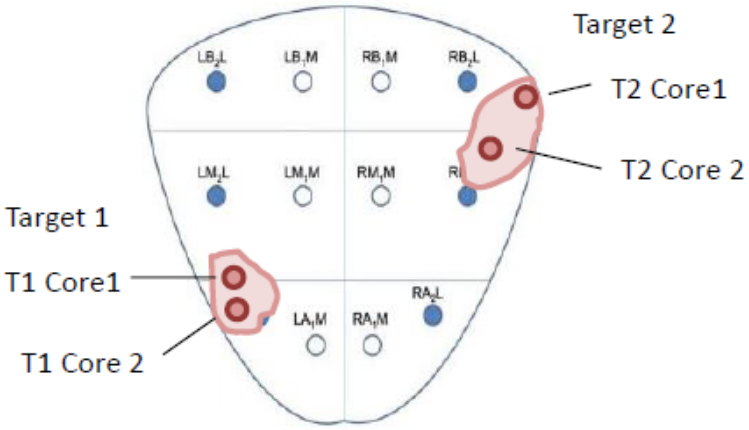


Biopsy Core	Acronym	MRI Location
Right Base Medial	RBM	1
Right Base Lateral	RBL	2
Right Middle Medial	RMM	3
Right Middle Lateral	RML	4
Right Apex Medial	RAM	5
Right Apex Lateral	RAL	6
Left Base Medial	LBM	7
Left Base Lateral	LBL	8
Left Middle Medial	LMM	9
Left Middle Lateral	LML	10
Left Apex Medial	LAM	11
Left Apex Lateral	LAL	12

Note: Use “A” (for Anterior) or “P” for Posterior to distinguish more than one target in same location if applicable.

Figure 2:

Naming convention for targeted biopsy cores



Targeted Biopsy cores (example naming convention)

Target 1, core 1
Target 1, core 2
Target 2, core 1
Target 2, core 2

The targeted cores are obtained from MRI defined regions of suspicion (shown here in red). Note that an MRI region of suspicion can overlap one or more of the standard cores.

*Recommend 4 cores per target with a minimum of 2 cores

Figure 3 EDRN MRI Flowchart