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A Description of Data Handling Practices and Software Tools Developed by the Boston Children's Hospital Echo Core Laboratory

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Abstract: Ultrasound 'Echocardiogram (echo)' images generated by commercial scanners are non-invasive, economical, and have therefore become an important clinical and research tool for cardiovascular disease. The Boston Children's Hospital (BCH, USA) cardiology department has developed echo image handling processes and software tools to simplify and manage the flow of echo data from sites participating in multi-center research studies. With frequent needs to correlate echocardiographic findings with surgical outcomes and more recently, better understand the acute and long-term effects of the SARS-CoV-2 pandemic on the heart in a multi-institutional collaborative [1], the need for a central corelab for image review and reporting has spurred the development of new software tools that seamlessly prepare, transmit and measure echocardiographic images and generate reports formatted to merge easily with clinical databases. In this paper we provide a descriptive guide to these software tools, and offer suggested approaches to data preparations that can simplify corelab processing.

Keywords: Echo Corelab, Health insurance portability and accountability act (HIPAA), Protected health information (PHI), Ultrasound images, Structured reporting.

1. Introduction: Echocardiographic Corelab

The advent of the echocardiogram (echo) as an economical and non-invasive imaging modality has provided new opportunities for multicenter research in cardiovascular diseases. In the early phase of echocardiographic imaging (pre 2000) most echo laboratories initially utilized video cassette tapes [2] to record and review echo exams that ranged in duration from 15 minutes to one hour. More recently, echo device manufacturers have adopted the Digital Imaging and Communication in Medicine (DICOM) standard [3] to enable digital communications across various devices and to allow for uniformity in imaging data interpretation using software that is specifically designed around this standard.

Fundamentally, an echo corelab is organized as a centralized facility to receive DICOM echo images performed by participating sites of a research network. Boston Children's Hospital (BCH) corelab has the capacity to handle data from 30 or more sites.

In the 20 years BCH has served as an echo corelab, nearly two dozen research protocols have been implemented, to generate publications on topics ranging from anatomy and pathophysiological effects of congenital heart disease [4], efficacy of pharmaceutical interventions [5], inter observer variability of measurement [6], and comparisons of outcomes from differing disease management strategies [7].

Multi-site research protocols can generate thousands of echocardiographic studies for management by the corelab. Each of these studies undergoes progressive stages of processing from initial scanning, to transmission and eventual reading by the corelab's echo technicians and echocardiographers. Each study received by the corelab is also checked and stored for easy access from a reading list. From a design perspective, at each of these preparation steps, implemented software should have the capacity to assign and recognize study identifiers (ID), ensure patient identifiers are anonymized, and to seamlessly transmit de-identified study echos for the corelab review [8] .

A standard corelab research project begins with the definition of research aims, followed by the enrollment of participating sites [9], development of subject inclusion/exclusion criteria, preparation of training materials, budget forecasting, and specification of software tools to be implemented at progressive stages of the research data pipeline [8]. These challenges require expertise from physicians with experience in the diseases being studied, as well as the supporting efforts by administrators, data managers, information technology (IT) professionals, and software engineers to implement needed processes and tools.

The echo corelab also works in close collaboration with a centrally administered data coordinating center (DCC). The DCC has responsibility for monitoring patient enrollments, developing maintained clinical databases, and managing the centralized channels of communication between participating sites of the research network [10]. The corelab's partnership with DCC includes creating training materials for image acquisitions and transfers. Additionally, corelab reports of measurement data are provided for upload to the study specific database at the DCC. This requires appropriate formatting of all corelab data for merging into databases maintained at the DCC.

2. Methods

2.1. Study Identifiers

Before a corelab protocol is implemented, it is helpful to have some estimate of: 1) The number of participating research sites; 2) The number of subjects to be enrolled, and 3) The number of echo studies to be performed on each enrolled subject. These preliminary estimates will determine the required storage capacity for the corelab, and allow for appropriate formatting of each study's identifier (Study ID).

Study IDs are designed to uniquely identify each recorded image set. The encoding of the study ID is vital to identify echo data through each stage of image processing, review, and reporting. BCH study IDs are encoded with these identifying components (Fig. 1):

Protocol ID : Protocol IDs are the component of the Study ID needed to link the dataset with the appropriate research project.

Site ID : Site ID's are a component of the Study ID needed to indicate the site from which the study was received.

Subject ID : Subject IDs are proxy references that can link to mapped patient medical records maintained by sites. For the corelab, the subject ID therefore provides a means to communicate with the site about a particular subject, without having to access the subject's private identifying information.

Time Point ID: Corelab protocols frequently consist of multiple follow-up echocardiograms for a given subject. Starting with a baseline diagnosis scan (scan 1), the subject might undergo multiple follow-up echocardiograms over a period of days, months or years. Each scan's placement in this follow up sequence is specified by the Time Point ID.

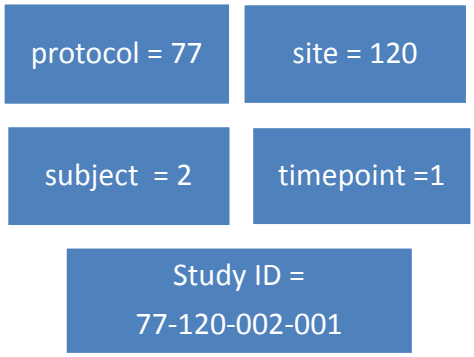

Fig. 1. The component factors, which uniquely identify each echo study include the protocol, site, subject, and time point.

The planning of anticipated site and subject participations is a key component of the Study ID's format to be implemented for a research protocol. For example, if participating site counts will not exceed 99, the format of the Study Id's site component can be limited to two digits. Similarly, if subject participation counts will not exceed 9999, then four digits of the Study ID's subject component will suffice to identify each subject.

2.2. Protected Health Information (PHI)

Since the introduction of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) [11], site research data provided to outside entities

needs to be 'scrubbed' of protected health information (PHI) that can reveal a subject's identity. With an echo data set, there are two basic types of PHI that need be removed at the site before the images can be transmitted.

The first type of PHI is found in the embedded pixels of each echo image, which may include textual information of the research subject's name or medical record number. With most image formats, this identifying information is visualized at the very top regions of the echo image, and is readily accessed for image redactions by software (Fig. 2).

A second type of PHI is found in DICOM tag elements which contain the metadata descriptions of each image file. These data elements include information such as the research subject's name, medical record number, address, telephone, or date of birth. Our laboratory has implemented a tool, which applies open source DICOM methods [12] to reconfigure PHI sensitive data elements by automatically de-identifying these elements with substitute or blank values.

In practice, techniques for PHI removal may be site specific and some participating sites may apply preferred software packages for the de-identification. Different sites may also have hospital specific PHI regulations related to types of information that can be released. However, to ensure compliance with HIPPA, the corelab always performs a final check to confirm that all PHI elements are redacted. An ideal solution for image preparations in the future would be a single software package suitable for all sites, irrespective of the echo platform used, standardizing the method of

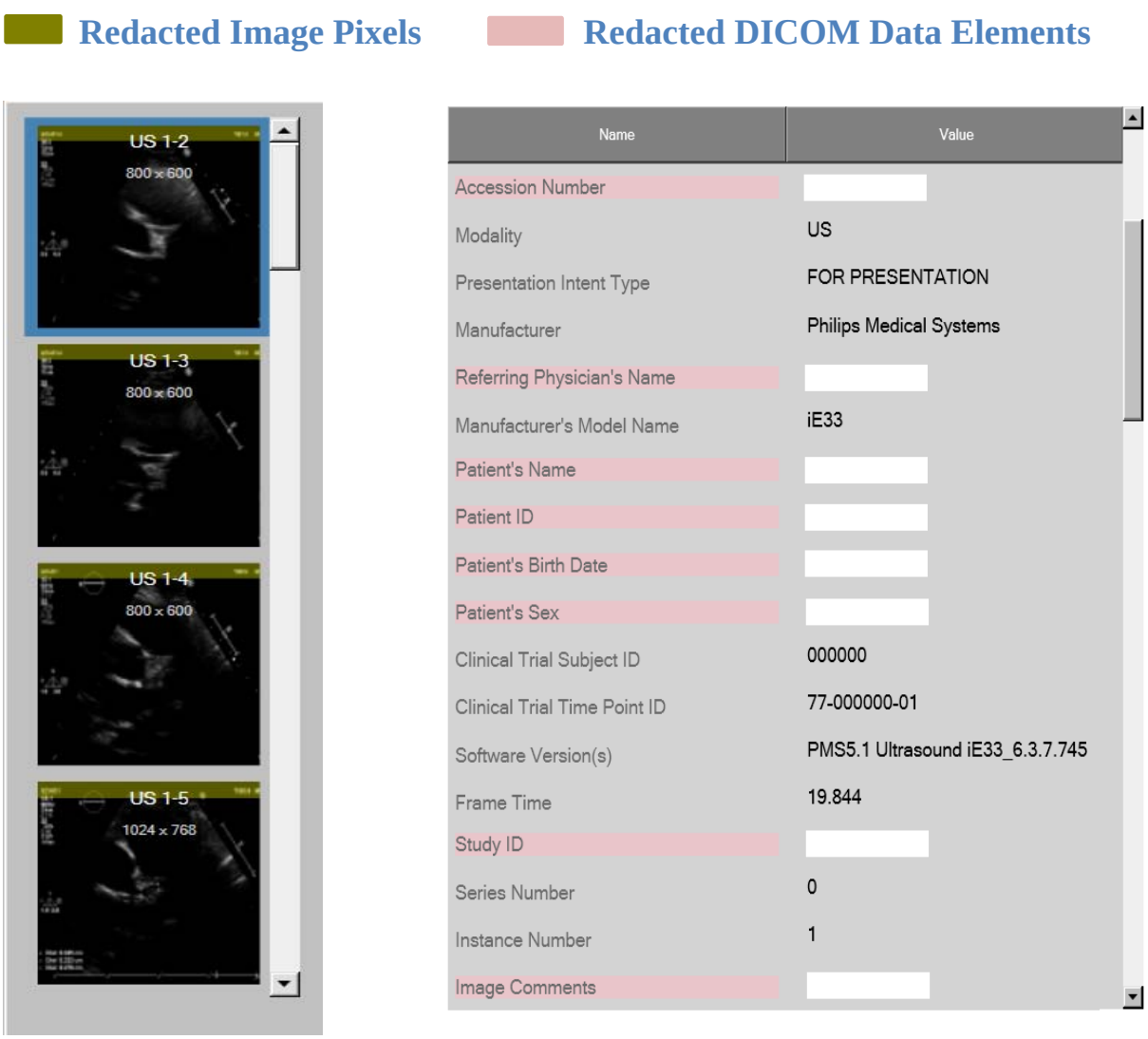

Fig. 2. Protected health information (PHI) is embedded as pixels in the echo images, or as the values contained within each image file's DICOM data elements. Pixels are redacted by manually identifying image regions containing PHI, and DICOM data elements are cleared by a configured automatic process to remove elements with potentially sensitive PHI.

image de-identifications by sites prior to the corelab transfer.

2.3. Patient Characteristics

In addition to removing PHI, the site will also provide metadata information for purposes of characterizing the study subject, and for inclusion of the data as part of defined subject categories. Information on age, sex, height, weight, blood pressure, or other vital data will allow for measures at the corelab to be normalized for statistical analysis. In a pediatric study there will be a spectrum of different ages and stages of developmental growth; thus, the normal ranges for a cardiac measure depend on factors such as age, height, weight, or body surface area. Standardization allows for the assessments of whether a measurement is within or outside of a defined normal range. Mathematically, these normative values are based on standard deviations from normal population mean, and are collectively known as measurement 'z scores' [13, 14].

2.4. Data Uploads From Sites

Once PHI data is removed, the sites upload images to a central and secure data server. For the images to upload, BCH has implemented a system for synchronization between echo data folders on site computers and objects of archiving systems contained within the Amazon Web Service (AWS) [15, 16].

The AWS archiving system is convenient for several reasons. First, the AWS upload occurs rapidly and reliably. As AWS is open source, needed configuration changes such as new user accounts, can be made by the corelab directly in the study specific space of the AWS system. Finally, for large studies the AWS storage system is cost-effective, and provides for a tiered storage pricing based on frequency of data access.

2.5. Image Transfers to the Corelab

From the AWS study archives, the corelab can download and review each study. However, prior to the downloaded study being released for review by the corelab reader, a quality assurance check is performed. When images are first received, preliminary checking procedures will compare image file counts with a manifest of expected files from a DICOM directory. If missing images are identified, then the site can be informed, and a data resend request might be activated.

After all study content is confirmed as received, each image is then tested to ensure that it is readable. Although the DICOM standard dictates a generic image format, DICOM accepts a wide variety of specific image formats, some of which may not have been previously encountered by the corelab's reading software. When a new format arrives that cannot be rendered by the existing software version, the software is modified and redesigned to accommodate the new image format.

Another important factor to be checked is to ensure that there has not been inadvertent 'mixing', which can occur if images from two or more study subjects (or study time points) have been combined into the same study data folder. To prevent study mixing, the DICOM standard's unique identifiers and study dates are assessed for each folder. If more than one study is indicated to be in the folder, the mixing indications are flagged to be further assessed and to consider that a resend might be appropriate.

The final check of received data is the visual inspection of images for PHI redactions that may have been inadvertently missed by the site's de-identifications. A typical echo study can have 100 or more images, and checking all the images can be labor intensive. To mitigate this, we have developed a system to automatically identify 'key images' containing PHI. A key image is a representative image in a format that is shared by other images in the study. Using this method, the redaction of pixels identified in the key image, can be automatically applied to the pixels of other image files with the same format as the key image.

2.6. Corelab Accession Numbers

When a study is checked and cleared for echo reading, the data are assigned with an accession number to specify the order of the study's arrival to the corelab. Starting with '1' (the first received study) the subsequent arrival of new studies from different sites will lead to progressively incremented accession numbers.

Accession numbers serve two important purposes. First, the accession number is an implicit connection to the counts of all studies received to date. The second feature of accession numbers is the simplicity the numbers provide to reference the study in ways that are more easily communicated verbally than the more complex study ID. The accession number becomes an effective pointer to a particular study at the corelab, while the Study ID contains supplemental data components with further details about the study, such as the originating site, subject number, and echo scanning time point.

There are two basic techniques for study accessions. An unstructured accession process will accept studies in the order in which they are received. A structured accession process will order study placements into the reading list in a specific way that might be guided by study protocols. For example, if a subject is to have three scanning time points and these scans are to be reviewed in sequence, then the studies are assigned three consecutive accession numbers. While structured accessions save time during the echo read, they are harder to implement.

2.7. Reading List Activation

The final step to prepare a study for the reading list is to activate a flag that will serve as an indication of the study's progress through the reading pipeline. At our corelab, these enumerated flags show the study's progress through the different stages of the review:

1) *Active Flag*: the study is in the process of being measured.
2) *Signed Flag*: the study measures are completed and ready for sending to the DCC.
3) *Sent Flag*: the study measures have been successfully transmitted to the DCC, and are locked from additional edits.
4) *Retired Flag*: the study measures are not to be sent to the DCC.

When the study is first placed into the reading list, the flag is set to 'active'. When all measures are completed, the study is 'signed' by the reviewer. Signed results are sent to the DCC and the 'sent' flag is applied. Studies indicated for withholding of data from the DCC are designated to be 'retired'.

3. Reviewing, Measurement and Reporting

3.1. The Echo Report

Corelab physicians and echo technologists apply a custom designed software program to render images and trace geometric tissue measurements as image overlays. These measures are presented to the reviewer as a checklist of items that form the content of each study's structured echo report. This report checklist will have been specified by the group of principal investigators with knowledge about the measures considered to be important and essential to fulfill the specific aims of the research. All needed measurements are then organized into the report as sections of a tree data structure that can be completed by reviewers as they read the echo.

Content of the echo report generally includes items that are classified into three basic categories: 1) Traced Measures 2) Calculations and 3) Coded Assessments. Each of these item types is configured in a similar fashion. First, the item of interest is selected from a dictionary of coded concepts [17] for inclusion into the report. The selected dictionary item is then characterized by its unique code to identify what will be reported. The item's presentation in the report's interface may also be customized and presented to the reviewer with a helpful guide to the intended measurement's anatomical imaging location. Measured content also has the specification of desired units, and display precisions. Finally, each item of the report is exported to the DCC with a unique database field code that is mapped directly to the DCC's master database.

'Traced' items of the echo report are based on the reviewer generated outlines drawn as image overlays. These measures might include point-to-point distance assessments (Fig. 3), or a measure of the heart chamber's cross-sectional area visualized from a 2-dimensional echo view [18]. Velocity of blood flows or tissue motions can also be quantified from the echo scanner's application of Doppler processing [19].

Calculated report items are automatically assessed by computing derivations based on the inputs provided from the tracing measures. Reported calculations might consist of the heart chamber's volume reconstruction [20], a ratio between two traced measures, or the statistical identification of a measurement outlier from an expected normal range [13].

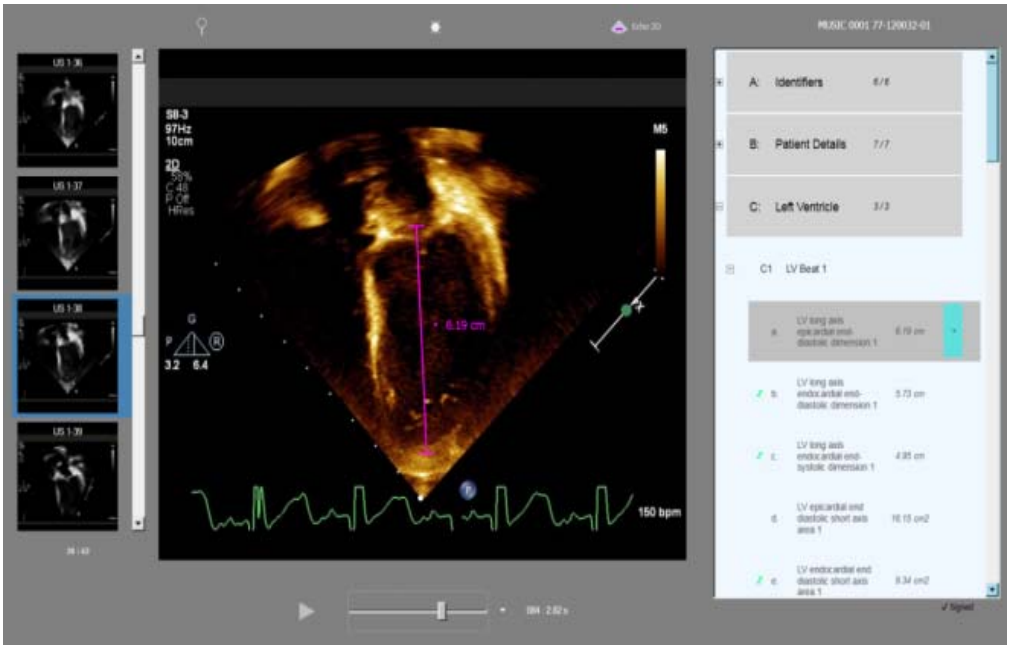

Fig 3. The dimension of a traced left ventricle long-axis is stored as one item of the echo report.

Coded report items are not measures per se, but are assessed as selectable options from a list. An example of a coded report item may be a reviewer's indication for the severity of a disease condition as either 'mild, moderate, or severe'. Each selectable option from the list will have a unique identifying code formatted for compatibility with database structures maintained at the DCC.

An important feature of each report item is the option to indicate if the item's measurement or assessment cannot be made. Generally, there are two reasons that a particular measurement or assessment might be incomplete. First, if the image of the heart structure to be visualized for the report item is not available from received images, the report item is said to be 'Missing', because the image is missing. A second cause of incomplete measurement may arise from poor image quality. In such cases, the reporting item result can be indicated as 'Indeterminate', i.e. the image is present, but a reliable assessment is nevertheless not possible.

3.2. Signatures and Exports

After measures are completed, the report is finalized with a signature from the reviewer. The study findings are then considered ready for inclusion with results from other completed studies into a dataset, which is exported to the DCC on a periodic basis. The exported data will constitute one key component for the analysis of study outcomes, and will form the comprehensive statistical basis of the research protocol's clinical recommendations. The DCC's statisticians and corelab personnel are then convened into study committees that review results and develop manuscripts for scientific publication.

4. Discussion

4.1. Designing Perspectives

Some aspects of the software features specifically designed for a corelab are very different from the features of a clinical software design. A clinical software program undergoes a rigorous Food and Drug Administration (FDA) approval for well-defined functional requirements in patient care scenarios. With a corelab application, the design and implementation of the software is more fluid and versatile, and has an ability to respond to needs that may not be anticipated at the initiation of the research protocol. Several changes to the software may be indicated after the corelab's review of initial image datasets. The software is then designed to rapidly accommodate any alterations that might be suggested by the new knowledge gained as the research project progresses. Some of these changes might include the addition of a measurement for echo reporting, or a modification to the imaging aims which can alter the process at the sites for imaging and data upload preparations.

With the goal to achieve software flexibility, it is useful to specify some of the critical functional details that will be the primary features shared by all corelab protocols. These critical features can then define the planning for effective and rigorous testing of the software. From the designer's perspective, the critical features also become more convenient to maintain, when the features can be partitioned from the other software elements that will be less critical for the research project.

To effectively manage corelab software, it is also important to understand which software features are to be hard coded (i.e. fixed and cannot be manipulated), and which features are to be user configurable for mid-stream protocol changes. Fixed features include the rendering of true image pixel colors, cine-image playback synchronization to a clock, and assured accuracy of traced measures when checked against calibrated standards. These basic and critical functionalities represent the essential components of the software needs for all research protocols. The more flexible aspects of designed software are ideally configurable in order to assist with protocol specific changes anticipated throughout the lifetime of the research project. A configurable item might include the addition of a new reporting measure, or some change to the Study ID format to handle growing patient enrollments and study counts.

Another practical and important design factor is to ensure all implemented software will be compatible with the various computer operating systems (OS) at the different sites of the corelab network. As some sites will have computers with a more recent version of the Microsoft Windows OS, it is prudent to choose which developed software features can be relied upon to perform for the various OS environments.

4.2. Process Considerations

In parallel to these considerations for design, the corelab's research output takes into account the linked processing between site image preparations, corelab reviewer measures, and the DCC's maintenance of research data. To facilitate a seamless integration between these stages of the corelab network, it is vital to provide some training of site personnel, and also test the corelab software capacities as early as possible with preliminary data validations. Early stage 'qualifying study' tests can then be applied to limited study counts and identify process or software changes to be made before large study influxes can be received. A test study process has now become standard practice for all stages of corelab data flow, including site image preparations, receiving area data handling, and structuring of echo measures forming the content of the study report.

4.2. Merged and Split Storage

The different types of files handled by the corelab include the image files of DICOM, together with echo

report files containing results of image measurement data. A typical echo study consists of approximately 100 DICOM images, and may consume over 2 gigabytes (GB) of disk storage space. By contrast, an echo measurement file is formatted in the Extensible Markup Language (XML), and is relatively compact at approximately 100 kilobytes (KB) in size. For most corelab protocols, the DICOM images and the XML report file of the study will be stored in the same data folder. This is a 'merged' method of data storage that is simple to maintain, and is preferred for simple corelab protocols with one read per study.

Some corelab protocols will have images that might undergo multiple reads by different reviewers. The measures between the reviewers will then be assessed for inter-observer variability. When multiple sets of measures are to be generated for the same image files, it becomes useful to consider 'split' data storage configurations, with reports generated by each reviewer stored into separate folders, which are linked to the shared location of the centrally accessible images. A split storage configuration is more complex to implement, but facilitates the review and export of measures to be generated by different reviewers.

4.3. Other Data Pipeline Models

The traditional model for a corelab network follows a data flow based on having sites provide images to a central reading facility. An implicit aspect of the centralized reading method therefore involves the de-identification of images by site data coordinators before the images can be uploaded. At the corelab, there is also a need to maintain significant resources to handle the gradual accumulation of all received site images which eventually reside on the corelab servers.

With the recent trends for economical 'cloud-based' data sharing, new possibilities are now introduced to simplify and alleviate the corelab's storage resource requirements. A cloud-based storage can allow for on-demand images to be downloaded for each initiated corelab study review session. When the study reads of the session are completed, the downloaded images can be purged from the corelab's server, greatly reducing the storage costs associated with a permanent local archive of the study. As more corelab projects are completed, a long term archiving of all image data (from all projects) is also economically achieved from a cloud-based storage.

Another corelab data exchange method to be considered, is to provide each site with reporting software designed to generate measurement results for a direct upload. In this 'distributed' study reading model, instead of receiving and reviewing images the corelab effectively functions to organize all the measurements generated by the site reviewers. The participating sites are then responsible for maintaining local image data, reviewing the images, and reporting measurement results with a periodic data send. With this envisioned data flow, the corelab only requires a minimal storage capacity for the received measures. Additionally, the distributed reads alleviate the need for PHI redactions prior to image transfers, because all images remain at the site location.

The choice between a centralized or distributed data flow will ultimately depend on the complexity and specific aims of the research study. Centralized reads will benefit from the quality assurance procedures that can be easily applied by the corelab's limited pool of readers. Alternatively, distributed reading methods provide for the assessments of measurement variation between sites and the distributed model is implemented at a reduced cost. It is also important to note that with the distributed review process, the results from the different site reviewers may be influenced by each site's image reading practices. Subsequently, some variation factors can be anticipated in the statistics of measures that would be gathered from different sites.

Summary

In this paper, we have provided descriptive guides to effective corelab planning, software component design, and data handling practices. For the purposes of planning and implementation, we suggest the initial steps to be considered for a new corelab protocol to include: (a) specification of the echo image views and measures needed for the research aims (b) preparation of training materials, (c) configuration of software for image preparations, transmissions, quality assurance checking, and reporting, and (d) a process to prepare measurements and related data in formats compatible with DCC records. The success of these linked data stages naturally benefits from engaged channels of communication maintained between the corelab, research sites, and the DCC.

As more sites from the US and other countries participate with corelab research, data pipeline handling capacities will need to be scaled and expanded to meet increasing image preparation, transmission, storage, and measurement activity needs. These factors will naturally spur the development of new software tools to distribute some of the corelab's current workload activity to the sites, where trained data managers and reviewers can independently apply image quality assurances and perhaps also perform site based measures. This envisioned distribution of corelab activity will be facilitated by improved software developments, and lead to cost effective and timely responses to arising public health research challenges.

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