Rare Diseases Clinical Research Network (RDCRN)
Data Management and Coordinating Center (DMCC)

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1. Introduction

Jeffrey P. Krischer, PhD is Distinguished Health University Professor and Chief of the Division of Bioinformatics and Epidemiology, Department of Pediatrics, University of South Florida College of Medicine and has been active in the design and conduct of clinical trials for more than 30 years. He is an internationally-recognized leader in clinical trial organization and data management. Dr. Krischer is the Principal Investigator of the Data Management and Coordinating Center (DMCC) for the ORDR, NCATS Rare Diseases Clinical Research Network and other NIH-funded networks for diabetes, and oncology.

The DMCC houses all data for the RDCRN centrally via in-house scalable and customizable electronic data capture systems; the DMCC system has collected and stores over 22 million data points. Some of the data systems built by the DMCC for the RDCRN include: internal members' only site with calendar, listserves, document navigation, comprehensive member directory with over 2400 Consortium members and 400 institutions, committee structure, multi-tiered security (protocol-based, user-based, consortium-based, folder-based security structures); specimen collection, shipment, and tracking system; pharmacy shipment, inventory, and dispensation system; randomization system; participant management system with electronic case report forms (eCRFs); (online) eligibility voting system; standardized and automated report sets (accrual, demographics, adverse events, compliance, study status) updated no less than monthly; automated XML/CSV data sets with associated data dictionaries; Adverse Event Data Management System (AEDAMS) for real time reporting, submission, review, and distribution of adverse events as they occur; and a Network Contact Registry.

The DMCC is funded by ORDR, NCATS and NINDS to provide a secure, customizable, scalable coordinated clinical data management system for the collection, storage, and analysis of diverse data types from clinical researchers working on many different types of rare diseases. In the first RDCRN grant cycle (2003-2009), the DMCC was funded by NCRR to provide statistical and project manager support for each of the 10 funded consortia. In the second grant cycle (2009-2014), each consortium was responsible for identifying an administrative core (project manager support) and statistical support; all 5 of the re-funded consortia from the first grant cycle entered into a sub-contract with the DMCC for the DMCC to provide the administrative core and statistical support. There were 19 consortia funded initially in 2009.

2. Project Management Support

The DMCC Project Managers review protocols and informed consent forms (ICFs) for essential elements and submit protocols and ICFs to the NIH for review. Contracting with the DMCC for additional administrative core (Project Manager) support includes monitoring site and protocol compliance, monitoring site and protocol accrual, hosting/running consortium and site coordinator calls, training sites, tracking IRB approvals, activating and tracking the status of protocols and sites, AE monitoring, drafting and reviewing/editing protocols, ICFs and data forms, data curation, providing direct contact and support to

consortium sites, etc. The DMCC has regulatory expertise with IND submissions, conducting international trials, submitting certificates of confidentiality, ClinicalTrials.gov registration and results submissions, good clinical practice, submissions to PubMed Central and creation and coordination of Observational Safety Monitoring Boards (OSMBs) and Data and Safety Monitoring Boards (DSMBs). The DMCC conducts the RDCRN Audit Program.

a. IND Submissions

The DMCC holds several Investigational New Drugs (INDs) and has submitted IND applications for many of the grants and protocols the DMCC supports. The DMCC has expertise in filing IND applications, completing 1572s, safety reporting, etc. The DMCC presented and taped a training session reviewing the submission of an Investigational New Drug (IND) application to the Food and Drug Administration (FDA). The training includes an overview of required forms, how to complete required forms, where to access required forms and the process for electronic IND application submissions. The training is posted to the RDCRN Media Center for on demand viewing reference.

b. International Trials

The DMCC has experience conducting international trials and can provide guidance on regulatory requirements, shipping requirements, human subjects research practices, pharmacy operations, etc.

c. Certificate of Confidentiality

Certificates of Confidentiality (CoCs) are issued by the National Institutes of Health (NIH) and are an important tool to protect the privacy and confidentiality of research study participants by protecting identifiable research information from forced disclosure. The DMCC has obtained several certificates of confidentiality that are maintained on file at the DMCC. The DMCC can provide guidance for submitting certificate of confidentiality requests to NIH including whether international sites should be included in the application, how to apply for a CoC for multi-site trials, if a consortium needs to apply for a CoC for each study, what studies should obtain a CoC, etc. The DMCC coordinated and facilitated the effort for RDCRN consortia to submit Certificates of Confidentiality applications to cover human subjects enrolled in RDCRN protocols.

d. ClinicalTrials.gov

All RDCRN studies are required to be listed on ClinicalTrials.gov. The DMCC can provide guidance on how to register a study to ClinicalTrials.gov, which studies are required by law to have results posted to ClinicalTrials.gov, and how to post results to ClinicalTrials.gov. The DMCC presented a three-part broadcast training session reviewing 1) an overview of the clinicaltrials.gov system and requirements; 2) registration to clinicaltrials.gov; and 3) results reporting to clinicaltrials.gov. The trainings are posted to the RDCRN Media Center for on demand future viewing reference.

e. Good Clinical Practice

All accruing RDCRN protocols are audited to look at protocol adherence, safety, data integrity and good clinical practice. The DMCC can provide guidance on the process of informed consent, essential documents, investigator responsibilities, drug accountability, electronic data capture, etc. The DMCC has training materials available on the Members' website that review all aspects of ICH E6 (Good Clinical Practice)

including 1) Overview of GCP, historical context, application and scope; 2) Investigator Responsibilities; 3) Sponsor Responsibilities; 4) Clinical Trial Protocols and Amendments; and 5) Essential Documents for the Conduct of a Clinical Trial. The DMCC Project Management staff is also available to answer any questions.

f. Training

The DMCC has the capability to record general, protocol or consortium specific training, post the training to the Media Center so users can view the training on demand, track who viewed the training and provide a training report for the consortium. The DMCC currently has Network trainings regarding online systems use and navigation covering subject registration and outcomes data reporting, adverse event reporting, treatment assignment and randomization, pharmacy system reporting, specimen system reporting, etc. as well as consortium and protocol specific trainings that the DMCC records and posts in collaboration with the Consortium.

g. PubMed Central

In accordance with the NIH Public Access Policy, papers resulting from the RDCRC U54 award need to be submitted to PubMed Central. Several journals either require the paper author to request that the paper is submitted to PubMed Central or do not have a mechanism in place to submit the paper to PubMed Central (in this case the paper author is responsible for submitting the paper to PubMed Central). The DMCC has a Medical Information Specialist (MIS) on staff that can assist PIs with determining who is responsible for submitting the paper to PubMed Central (journal, paper author or both), and if needed assist the PI with the paper submission to PubMed Central. The MIS can also help the PI determine if he/she is in compliance with the NIH Public Access Policy.

h. OSMB/DSMB

The DMCC has experience putting together OSMB/DSMB rosters and serving as the executive secretary for OSMB/DSMBs. As part of the executive secretary role, the DMCC polls board members for availability, collects conflict of interest forms, prepares the agenda, coordinates honorarium payments, drafts the minutes and determination memos and works with the board chair to receive approval on the minutes and determination memos prior to distributing them to the study team. The DMCC also works with the study team to prepare the team for the OSMB/DSMB meeting including receiving study chair comments and/or presentations prior to the meeting.

3. Biostatistical Support

The DMCC can subcontract back to the Consortium to provide the statistical support for one or more protocols including protocol development support and/or analysis support. The DMCC creates several standard Network, Consortium, protocol and site reports for all consortia and has the capability to create customized reports.

a. Protocol Development Support

Protocol development support includes participating in protocol study design, and the identification of scientific objectives, study end points, target accrual, etc. The DMCC would also participate in Data and Safety Monitoring Board (DSMB) meetings and calls on the Consortium's behalf.

b. Analysis Support

Analysis support includes conducting analyses for presentations and publications, querying the data, supplying data sets, producing study progress reports for investigators and the DSMB, producing specialized consortium, protocol and site compliance, error and monitoring reports.

c. Network Reports

The DMCC routinely prepares reports describing study progress for the NIH, consortia, clinical centers, committees and Protocol Industry Sponsors. Standard protocol reports are generally updated at the end of each month and are available on the RDCRN members' web site. Examples of reports generated include: protocol status reports, accrual reports, adverse event reports, demographics and race/ethnicity tables, contact registry enrollment reports and related usage.

The DMCC has developed several standard reports which are available on a Network, consortia, and study level. These reports monitor the status of enrollment, subject eligibility, frequency of reported AEs, as well as demographics, race and ethnicity and are added to the Members' website; each time a protocol is activated, Network and consortia level reports are updated and study level reports are added to the Members' website. The main members' webpage includes an accrual table which details real-time accrual across all consortia and studies in the Network. Reports are used by consortia to review progress and address the frequency and incidence of Adverse Events by study as well as to fulfill IRB and related regulatory submission requirements.

d. Compliance Reports

The DMCC creates and regularly runs standardized compliance reports for all consortia that automatically post to the RDCRN member's website monthly. These reports assist the DMCC and the consortia site staff in monitoring data analysis issues, accrual, data entry, form completion, protocol version control, Contact Registry accrual, and training status. The DMCC provides compliance reports on a consortium, protocol and site level. Consortium level reports provide a global picture of consortium compliance and include all protocols and all sites within a particular consortium. The protocol specific compliance reports provide overall compliance for each site within each protocol in the consortium. The site specific compliance reports per protocol provide detailed information to the sites so that they are aware of what data is delinquent and still pending. Compliance reports are an essential piece of data management within the RDCRN and are used by the consortia for reporting to the IRB and DSMB.

e. Error Reports

The DMCC posts error reports at the consortium level and institution level. The reports check for standard items (missing DOB, Age at Registration < 0, missing Race, Gender and/or Ethnicity), but can be expanded and customized to include either Network wide or Consortium specific errors. The reports are run on a regular basis and posted on the Members' website for each Consortium.

f. Custom Reports

The DMCC can create custom reports at the Consortium, protocol or site level.

4. Development Support

The DMCC has a team of software developers that create Network and Consortium applications as requested by ORDR, NCATS, the NIH institutes supporting the RDCRN, the

RDCRN Steering Committee and/or individual consortia. The DMCC is funded by ORDR, NCATS and NINDS to provide a secure, customizable, scalable coordinated clinical data management system for the collection, storage, and analysis of diverse data types from clinical researchers working on many different types of rare diseases in geographically disparate locations.

The software applications developed by the DMCC comply with 21 CRF part 11 and utilize numerous methodologies and constraints to confirm data integrity, complete data audit trails, and authenticity. The DMCC utilizes compound methodologies to trace changes to data in the system.

The DMCC also has a mechanism in place to receive data from other databases.

a. Electronic Case Report Forms

The DMCC works with consortia to develop electronic case report forms (eCRFs) which can be accessed online through the DMCC's secure website anywhere in the US or the world. The DMCC has a library of standard forms available to each consortium; consortia can add or remove fields to the standard forms. In addition, consortia can design specialized data forms. The DMCC works with study chairs to gather requirements to develop specialized eCRFs, using existing forms and other sources of manual data capture to craft the final eCRFs. The DMCC works closely with the consortium Principal Investigator and Project Manager to review the source forms and make suggestions for either streamlining the data collection, or updating the forms and associated eCRFs to ensure correct data collection.

To help track data compliance, the DMCC can designate "required to save" or "required to complete" options on each data field on each individual case report form. The required to save and required to complete options are related to the protocol study outcome data.

i. Smart Forms

The DMCC has extensive experience with form development and has the capability to create smart forms. A 'smart' form displays or hides current fields based on criteria determined by the study chair. For example, if patients with multiple diseases can be enrolled into one protocol, the form fields may change based on the disease type or gender of the participant enrolled.

ii. Data Linking

The DMCC has developed technology to link data across common forms across protocols. When an eCRF is utilized by multiple protocols the participant's form data can be linked from one protocol to another. This improves the integrity and efficiency of the data as the form data is only entered once. This also saves site coordinator time since the data does not need to be entered multiple times.

iii. Data Standards

The DMCC has established Network data collection standards that are compliant with emerging Federal and global recommendations. The Network standards serve as a framework for cross-disease data mining efforts as well as to establish a resource for the broader audience of investigators for whom data sharing is directed.

Adverse Event Data Management System: This standard was developed to facilitate AE reporting across the spectrum of RDCRN studies (observational to controlled clinical trials), and includes specifications for definition, coding, and communication of potential adverse events, as well as for Network-wide analysis and action following reported events.

Medication Coding: The Network uses RxNorm to code medications. RxNorm is the U.S. standard developed and supported by the National Library of Medicine. The Medication data for RDCRN studies is collected as granularly as possible – at the level of medication product (brand) or generic ingredient. RxNorm fields are collected on the Network Medication form along with the name of the drug entered by the user. Once the user enters the medication name, the RxNorm database is searched to select the matching RxNorm code. The RxNorm relationships allow data to be grouped by different levels of specificity (i.e., medications coded by brand name can be queried by the active generic ingredients). Since there are many different names for medications (brand name in US, brand name in Europe, generic name, etc.) the RxNorm coding system is the mechanism used to group all of the medications (at whatever level the user is interested including name or ingredient) in the database in a uniform way. Additionally, the DMCC pairs the RxNorm codes with the MeSH pharmacological action classes and merges the data into the RDCRN data sets.

Clinical Health Information: The DMCC uses the Systemized Nomenclature of Medicine – Clinical Terms (SNOMED-CT) to standardize clinical findings, anatomy and procedures across the RDCRN. SNOMED-CT codes are collected on physical exam or medical history eCRFs along with the clinical finding, anatomy or procedure entered by the user. The eCRF will provide several possible SNOMED-CT codes that the user can select to match the clinical findings, anatomy and procedures that best fit the participant. This allows local variation in terminology use, but stores the final study data in a uniform way. For example, the terms HA, headache, and pain in head would all be stored in the database in a uniform way.

Other Data Standards: The DMCC routinely uses data standards consistent with the Consolidated Health Informatics (CHI) initiative, the National Health Interview Survey and the Office of Management and Budget (OMB). The DMCC encourages the use of structured data over free-text wherever possible. Free text (un-coded) data has limited value for analysis.

iv. Tracking System

Each eCRF developed by the DMCC has a tracking system associated with the form. The purpose of the tracking form is to track data compliance. The tracking form can be used to indicate if an event is done or not done. The tracking system is used to indicate the data is done when data has been collected but is not available to enter into the form; for example if labs will only be analyzed at the end of the study or when a certain amount of samples have been collected. The tracking system is used to indicate data is not done when data is not required per protocol, for example PFTs are only required for children 6 and older, or when data will not be collected, for example if the participant missed the appointment.

b. Participant Scheduling

The DMCC has developed a sophisticated system to manage participant scheduling according to the rules of a protocol and can limit the display of scheduled eCRFs (or portions thereof) based on a study participant's age, gender, eligibility status, or other criteria. The event schedules can also be programmed to limit data entry prior to eligibility, randomization or baseline study visits (as determined by study chair and/or protocol). Additional logic can be incorporated into this dynamic scheduling system to handle studies with irregular visit schedules, "flare" visits, and multiple dosing regimens within the course of a single study.

An example of a dynamic visit schedule is a study that contains multiple treatment arms each with dynamic scheduling. Per protocol, participants switch between treatment arms as they receive multiple treatments over the course of their disease. As the treatments are given, the participant is switched from one treatment arm (and schedule) to another treatment arm (with associated schedule), with the expected events for the new schedule replacing those for the previous schedule. These "switches" in treatment arms are not mutually exclusive, with participants able to switch back and forth between treatment arms as treatments are repeated. This type of complicated scheduling is not typically needed for most protocols but is something that the DMCC has the experience and capability to implement.

c. Data Sharing

The DMCC data outcomes system (electronic data capture) allows for multi-level security- which enables consortia to view but not alter data collected at a different clinical center within the same consortium. Additionally, when/where applicable Personal Health Information (PHI) is suppressed to ensure privacy and confidentiality are maintained. Posted/automated data sets are posted by the DMCC within each consortium's secure resource page; only individuals identified by the consortium PI or consortium site PIs as authorized individuals may access the consortium page on the Members' Website.

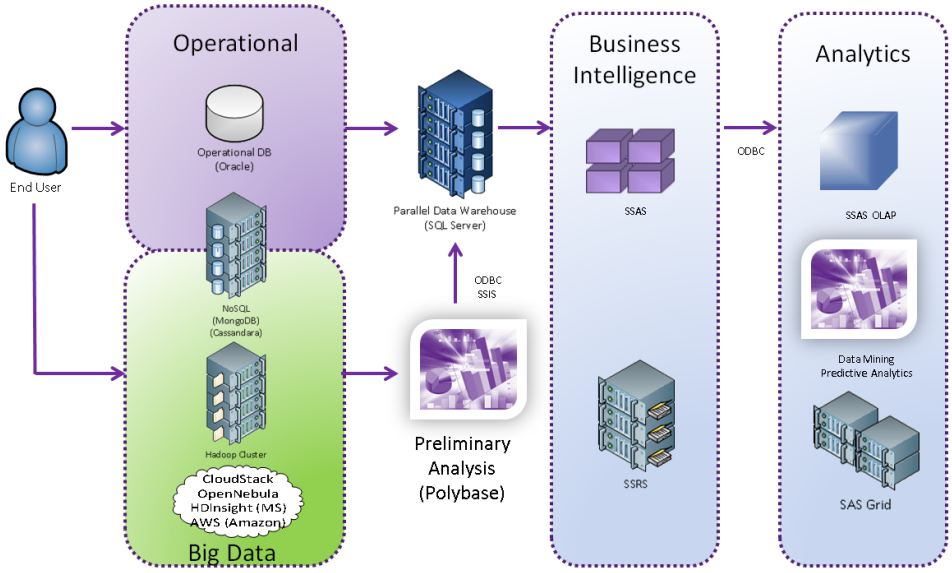
d. Big Data

The Data Management and Coordinating Center (DMCC) architected a Big Data and analytical infrastructure to facilitate large structured and unstructured data. Big Data comprises of large multifaceted structured and unstructured datasets that are excessively complex to manage with normal database management tools. The DMCC has the capacity to receive vast amounts of large datasets and specializes in the areas of life science data including genomic, proteomic, and metabolomic. The underlying Big Data infrastructure is a horizontally scaled system that utilizes a state-of-the-art computational distribution system. The foundation of the architecture employs Apache Hadoop and NoSQL databases to facilitate Big Data administration and analysis. Tools such as SAS and R are used for deep analysis of complex big data. External organizations can transmit Big Data to the DMCC in a variety of methods including HTTPS, SFTP, Private Cloud, and Virtual Private Network.

The business intelligence tier of the Big Data architecture comprises of a data warehouse that delivers performance and scalability through massively parallel processing. The data warehouse is highly scalable with high data transfer speeds. It consists of a hub and spoke architecture providing business users with the ability to keep existing data marts to suit their needs. Integration Services transforms, migrates,

and integrates the data across various platforms including Hadoop and the data warehouse.

The analytics tier of the Big Data architecture comprises of online analytical processing (OLAP), data mining predicative analytics, and the SAS Grid. OLAP cubes are data structures that aggregate the measures by the levels and hierarchies of each of the dimensions to be analyzed. Data Mining is an analytical process used to explore data for consistent patterns and systematic relationships. SAS Grid is a centrally managed grid computing environment that incorporates distributed processing, load balancing, and scaling to vastly improve the performance and run time of analytic processing.



e. Adverse Event Data Management System (AEDAMS)

The DMCC designed a dynamic adverse event data management system (AEDAMS) which allows sites to report and receive adverse event (AE) reports electronically in real time. When an AE is reported in the system, the participating sites and if applicable Medical Monitor, DSMB and/or study sponsor, receive an email notification with the AE report in real time. AE email notifications sent to the Medical Monitor can be reviewed electronically and if necessary can notify the study chair that a DSMB review or change to the protocol/ICF is warranted. Once the Medical Monitor reviews the AE, sites receive a review notification email in real time for submission to local IRBs. The system follows the FDA definition of seriousness (21CFR312.32) and utilizes smart CTCAE coding in which sub-categories are filtered by user selected category.

f. Specimen Management System

The DMCC designed a specimen management system (SMS) to track sample collection, shipment and receipt. The specimen management system tracks specimens at the participant and visit level and is used to track specimens from site to lab and/or repository. The SMS enforces rules defined by the study chair including only allowing specimens to be shipped to configured destinations and not allowing the shipment of a damaged specimen. The SMS provides site and lab staff the capability to collect, ship, receive, and upload test result data related to a specimen sample. Collection types and volumes, shipping routes, notifications and other study-specific information are configured for each individual protocol as they are implemented within the system.

Additionally, this modular, dynamic system furnishes customizable validation such as barcode duplication restriction and barcode range checks. The specimen barcode acceptance can be customized per sample type (urine, blood, etc.) as quality assurance that each barcode or identification number correctly corresponds with a sample type. Once specimens are shipped, an email is generated to the receiving lab and/or biorepository personnel to indicate the expected arrival date, participant ID number, visit time point and barcode or identification number that corresponds to the sample. A shipping list is also generated that the site can print and include with the shipment. The SMS provides specimen real-time traceability as members can track the current status and location of a specimen as well as the specimen's history.

There are many different labs and biorepositories throughout the Network that the DMCC works with and each has different requirements and capabilities requiring specialization. We work with the individual consortia and study chairs to gather requirements to develop a specialized SMS for each protocol to ensure the specimen route, specimen data upload, specimen shipment and specimen receipt is a seamless process for the sites and labs.

g. Pharmacy Management System

The Pharmacy Management System designed by the DMCC is made up of four modules: Treatment Assignment, Dispensation, Pharmacy Inventory and Dosage Management. A protocol can use all or one of these modules. The Treatment Assignment module can be based on a randomization block (protocol or site specific), be stratified by disease type, weight, age, etc. and can consist of assignment of a study drug or a study drug with a specific dosage and/or supplies. Treatment assignment can occur once or multiple times throughout a protocol. Blinded or unblinded treatment assignment notifications are sent to pharmacy personnel in real-time and include the participant ID, site, visit time point, and treatment assignment (when appropriate).

The Dispensation module notifies the central pharmacy when a treatment is given to a participant by a particular site so the pharmacy can send additional supply to the site. The Pharmacy inventory module assigns participants a treatment kit or bottle number based on treatment assignment to maintain blinding at a site. This module can also 'reserve' kits or bottles for participants and can be paired with the Dispensation module to notify the pharmacy when a site is low on a kit of bottle type. The Dosage Management module allows a Medical Review officer to make changes to a participant's drug dose based on lab readings or other means electronically through the system.

There are many different pharmacies throughout the Network that the DMCC works with and each has different requirements and capabilities requiring specialization. The DMCC works with the individual consortia and study chairs to gather requirements to develop a specialized Pharmacy Management System for each protocol to ensure the treatment assignment, drug dispensation, pharmacy inventory and dosage management is a seamless process for the sites and pharmacies.

h. Randomization

The DMCC has the capability to implement randomization as part of the secure RDCRN members' website. The randomization time point(s) will be dictated by the protocol and/or the study chair. For randomization at baseline, the clinical site personnel will confirm eligibility and verify that the participant has signed informed consent (and

assent when applicable) prior to the system randomizing the participant. Site study staff will be notified through the application that randomization has been assigned (randomization confirmation will note treatment assignment at unblinded studies or time points; randomization confirmation will not include treatment assignment for blinded studies or time points). Randomization can occur once or at multiple time points throughout the study. Prior to each randomization, the site staff will need to verify that the participant is eligible to continue in the study. For protocols using the Treatment Assignment module, the randomization assignment will trigger a real-time email notification to the pharmacy with the participant ID, site, visit time point, and treatment assignment.

i. Image Upload

The DMCC image upload system is integrated into the RDCRN member's website. The system provides members with the capability to upload multiple image files such as CT, MRI, ultrasound, etc. that typically utilizes DICOM compression. If DICOM is used, a service de-identifies the DICOM file so no patient identifying information is stored by the DMCC. The image system provides the end user with several upload options. The first option is for smaller files and the second option is for larger files, such as files that exceed 25 megabytes. For larger files, the system utilizes state of the art technologies such as SilverLight, C# and customizable Http Handlers that allow large files to be streamlined to the DMCC file servers in chunks. This efficiency allows the system to handle large image file uploads without placing excess load on the web servers and provides the end user with real time data transfer rates. Once an image is uploaded to the system, the user can view and download the images from the RDCRN member's web site. The large file upload streamlines the users experience and improves file transfer efficiency. The user receives instant feedback when the file upload process starts, can see the real-time file upload progression, and has the ability to asynchronously upload multiple files within the same session.

i. Full face images and video

The DMCC has the capability to accept full face images and videos of participants without a breach in confidentiality. Full face images and videos are stored in the secure database to which access is limited and files may not be opened or viewed without prior approval and prior notification and consent by investigators and participants. The DMCC stores the images as the central data repository for the RDCRN and collates the images for future transfer to the ORDR, NCATS designated data repository. The DMCC has approval from the USF IRB to accept full face images and videos.

ii. Stripping files of PHI

The DMCC has developed an automated system by which images (e.g. x-rays) are stripped of personal health information (PHI) to ensure no data is sent to the DMCC (in any format) that contains PHI (unless prior approval from the participant, site and the USF IRB has granted approval for the receipt of PHI). All DICOM images that are uploaded to the RDCRN Members' website are generally de-identified by the site before being uploaded. The DMCC automated system application opens the DICOM image file and checks the header strings for all the fields that normally contain identifying information (e.g. name, address, etc.). If this application finds any such information in any of the specified fields this information is stripped and overwritten with a blank or black space. The participant

id which is locally generated by the protocol manager tool is written into the name field which associates the image with the participant.

j. Interactive Voice Response (IVR) System

The Interactive Voice Response (IVR) system was designed by the DMCC to collect study data over the phone. The system allows end users (clinical staff and/or participants) to interact with the RDCRN Members' website on a daily basis via a telephone keypad by providing the user with simple menu choices provided by the system. When the participant calls the toll-free number, the participant receives a welcome message and then is prompted to enter in the study number and participant ID. The IVR system detects dual-tone multi-frequency (DTMF) signaling phone keypad inputs and responds with dynamically generated audio to direct users on how to proceed. The information entered into the IVR system by the participant is stored in an eCRF on the RDCRN Members' website and is assessable by site staff. The system has the capability to send e-mail notifications to alert staff when a participant has not logged into the IVR system so the site can follow-up with a phone call reminder to the participant. The IVR system is scalable and designed to accommodate large call volumes. The IVR system is utilized globally and in multiple languages such as English, Italian, French and Spanish. The IVR system has been used as a daily symptom diary to track disease episodes. Technologies utilized by the IVR system include voice over IP (VoIP), Microsoft Speech Server, Microsoft Office Communications Server, C# and Oracle.

k. Regulatory eBinder

The Regulatory electronic binder (eBinder) is an online system that stores essential study documents by protocol and site. The documents are assessable online by the site, Consortium Project Manager, NIH, the study sponsor and the DMCC. The essential documents are inclusive of (but not limited to) the following: A) Submitted by the site: All IRB approvals and related submissions (original submission documents to the IRB) and correspondence (approval letters from the IRB, letters requesting changes from the IRB, and PI responses to the IRB); all IRB approved consent documents; all Site Delegation Logs (SDLs); all CVs, medical licenses, Human Subject protection education Certificates (HSCs) for all individuals listed on the consent and/or Site Delegation log; all FDA documents (1572s, MedWatch reports, etc.); all required regulatory authority(ies) authorization/approval (CTEP, NIH, FDA, IBC, RSC if applicable); all DSMB or PRC correspondence (if applicable); normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol at the start of the study and updates during the conduct of the study (if applicable); certification/accreditation for medical/laboratory/technical procedures/tests at start of the study and updates during the conduct of the study (if applicable); B) Already generated by the DMCC: audit/monitoring visit reports; sponsor and/or DMCC correspondence including: letters, meeting notes, notes of telephone calls. The Regulatory eBinder can be used for remote auditing of essential documents and to give NIH and/or the study sponsor the capability to view all protocol and site documents on demand.

l. Eligibility Voting System

The DMCC designed, architected, and developed an eligibility review and voting system to give study staff the capability to "vote" on a subject's eligibility and then make the final decision via committee conference call. The system captures the participant's

eligibility criteria and sends automatic email notifications to the study voting panel. The system monitors the votes received and manages the workflow by sending notifications to the consortium project manager if the votes are not received in a timely manner. After all votes have been received, the project manager can review the votes, override them, or validate them based on the committee decision. This mechanism provides consortium members assigned to voter and project managers roles the ability to determine the eligibility status and stratum of a participant based on thorough review of the participant's data and a tallied vote. The system utilizes sophisticated technologies such as C#, NHibernate, ExtJS and WCF.

m. Data Transfer Agreements

The DMCC has developed a procedure by which data can be transferred from Federated databases to the DMCC for Consortia that have established data capture mechanisms in place. A Data Transfer Agreement (DTA) is set up with the consortia which defines the frequency for the data transfer and identifies who will receive the data acceptance or error notifications from the DMCC. Data is transferred to the DMCC via a secure FTP. DTAs are set up at the protocol level so consortia can utilize a DTA for some of their protocols and use the DMCC systems for other protocols.

5. RDCRN Public Website

The RDCRN Public Website serves as a portal for the rare diseases community, including patients and health care professionals, to provide information on research on rare diseases, consortium activities, RDCRN protocols and practice guidelines, the individual consortia websites and the over 240 diseases currently available through the RDCRN Contact Registry. All consortia are publicly represented on the RDCRN public website through a web page dedicated to each consortium that contains key information such as: diseases being studied, open protocols, participating sites, site contact information and Patient Advocacy Groups (PAGs) associated with the consortium. The DMCC works with each consortium to design a consortium logo (if the consortium doesn't already have one) and website aesthetics. The RDCRN public website had over 600,000 visits in the last year.

6. RDCRN Contact Registry

The RDCRN Contact Registry is a mechanism for patients to register themselves or a member/members of their family who have been diagnosed with a RDCRN-studied disease or disorder. The Contact Registry provides ongoing contact to each registrant, providing information when studies are activated, new sites open and/or about consortia or PAG sponsored events. The registrant can elect to share his/her contact information directly with the consortium studying the disease and/or Patient Advocacy Groups (PAG) so that he/she may be contacted directly by the Consortium and/or PAG. The registrant also has the opportunity to participate in Consortium or Network-wide studies conducted online.

a. Protocols

The DMCC has the capability to conduct protocols via the RDCRN Contact Registry using a participant user interface to allow participant data entry directly into the RDCRN Members' Website. The DMCC works with the Consortium to review the protocol, questionnaire(s), ICF and recruitment emails and then submits the study materials to the USF IRB. The DMCC will then send out an email(s) to participants in the Contact Registry that fit the protocol inclusion criteria. The email contains a description of the study and a link that takes participants directly to the ICF and survey. The DMCC has complex technology in place that allows participants to complete multiple

questionnaires at different time points, submit follow-up questionnaires based on responses to previous questionnaires, send out reminder emails, etc.

b. Research Update

The RDCRN Research Update is an application where subscribers (clinicians, research scientists, health educators, policymakers, or other interested advocates and supporters) can sign up to receive information from the RDCRN and Network consortia via e-mail. This application makes it possible for the RDCRN and Network consortia to distribute pertinent research and disease information to these subscribers. Potential subscribers sign up through a dedicated portal through the RDCRN Public website. Subscribers can elect to receive monthly email communications for one or multiple consortia.

7. RDCRN Members' Website

The RDCRN Members' Website is a secure, password-protected website for Network members that includes announcements, calendars, protocol management tools and electronic case report forms. Among the functions supported include systems for adverse event reporting and monitoring, research pharmacy drug management, biospecimen tracking, image processing, desktop videoconferencing, and automated reporting. Each Consortium has a dedicated page on the Members' Website.

a. Consortia Web Pages

The DMCC maintains a consortium-specific internal resource page and document management area for all consortia. The internal resource page allows user-level, group-level, folder-level, and protocol-level security as well as customizable group membership access levels (none, read, write, administration). The consortia resource pages/websites can be used to post meeting information, protocol documents, share data and reports. Additionally, the consortia can post events, meetings or calls to the consortium calendar, add and maintain consortium specific folders and email other members of the consortium or user defined subscriber/group lists through the resource pages. The Members' website is where sites enter data, report adverse events, etc. for each study.

b. Coalition of Patient Advocacy Groups (CPAG) Web Page

The DMCC maintains an internal resource page and document management area for the Coalition of Patient Advocacy Groups (CPAG). The CPAG resource page/website can be used to post meeting information, documents and to share common resources; the page allows for group-level and folder-level security. Additionally, the CPAG can post events, meetings or calls to the calendar, add and maintain specific folders and email other members of the CPAG.

8. RDCRN Audit Program

All accruing RDCRN studies are audited by the DMCC per the RDCRN audit guidelines. The RDCRN audit guidelines are in accordance with the NIH NCI-CTMB guidelines for monitoring of clinical trials for cooperative groups, located at http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm, last revised October 2012. Audit site visits comprise of review of regulatory compliance including IRB documentation and informed consent content, participant case records, pharmacy operations, and IND accountability (as applicable).

9. Resources

a. Library of Standard Forms

The DMCC maintains a library of standard forms available to the RDCRN consortia that includes a demographics form, medical history form, lab results form, physical exam form, concomitant medications form, etc. to aid consortia in developing study data forms.

b. Protocol template

The DMCC maintains a Network protocol template which includes information on electronic case report forms, the AEDAMS system, specimen management system, etc. and is in adherence with OHRP, FDA and GCP guidance regarding clinical trial and protocol design.

c. Manual of Operations template

The DMCC maintains a Network manual of operations template which includes sections on study personnel responsibilities, steps to activation, recruitment procedures, visit procedures, description and instructions, ICF process and procedures, data management standards, eCRFs, adverse event reporting standards, timeline and procedures, protocol manager tools, specimen management and specimen tracking.

d. Media Center

The RDCRN Media Center contains protocol-specific training presentations, system-related training presentations, Network and Consortium presentations made during meetings and conference calls, etc. Access to trainings and presentations is based on user security and roles assigned. The DMCC maintains a training report which tracks required training per Consortia and protocol.

e. GoToMeeting Web Conferencing

GoToMeeting is a web conferencing software maintained by the DMCC and available to the Network. GoToMeeting allows Consortia to host conference calls remotely but still interact with other members of the consortia through webcams and microphones. Call participants can share their screens with the other participants on the call to view PowerPoint presentations, applications, or use the drawing and editing tools to edit protocols or other documents. The GoToMeeting functionality is used for DSMB meetings to review progress reports and present new protocols.

f. RDCRN Overview and Consortium-Specific Slide Sets

The DMCC partnered with the Network's Strategic Planning Committee and designed, drafted, and finalized a standard Power Point slide set for each Consortium. The Standard Slide Sets are PowerPoint presentations that contain both Network and consortia specific information and statistics. The slides are automatically updated on a monthly basis and are available for download from the RDCRN Members' Website. The slides are completely customizable and can be modified to meet each consortium's needs, but serve as a consistent foundation for presentations given by the RDCRN consortia. The slide sets are reviewed and updated by the DMCC on a constant basis to ensure all information and reports are accurate.