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THE NATIONAL MDS STUDY

MANUAL OF PROCEDURES

Version 9.0 dated June 01, 2023

Sponsored by the National Heart, Lung, and Blood Institute
In collaboration with the National Cancer Institute

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1D	One dimensional
AML	Acute Myeloid Leukemia
ANA	Antinuclear antibody
APL	Acute Promyelocytic Leukemia
ARNP	Advanced Registered Nurse Practitioner
BBRB	Biorepositories and Biospecimen Research Branch
BioLINCC	Biologic Specimen and Data Repositories Information Coordination Center
BM-MNCs	Bone marrow mononuclear cells
CAP	College of American Pathologists
CBC	Complete Blood Count
CIBMTR	Center for International Blood and Marrow Transplant Research
CIRB	Central Institutional Review Board
CL/B	Central Laboratory/Biorepository
COI	Conflict of Interest
COR	Contracting Officer's Representative
CRFs	Case report forms
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTSU	Cancer Trials Support Unit
CV	Curriculum Vitae
DBDR	Division of Blood Diseases and Resources
DCC	Data Coordinating Center
DCP	Division of Cancer Prevention
DIN	DNA integrity number
DM	Data manager
DNA	Deoxyribonucleic Acid
EC	Executive Committee
ECOG-ACRIN	ECOG-ACRIN Cancer Research Group
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EPO	Erythropoietin
EQ-5D-5L	Euro QOL – 5 Dimensions – 5 Levels
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
FISH	Fluorescence in situ hybridization
FLAER	Fluorescein-labeled proaerolysin
FTP	File transfer protocol
FWA	Federalwide Assurance
H&E	Hematoxylin and eosin
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
IAM	Identity and Access Management
IATA	International Air Transport Association
ICU	Intensive care unit
ICUS	Idiopathic cytopenia of undetermined significance
ID	Identification
IDF	Supplemental Investigator Data Form

IRB	Institutional Review Board
ISBER	International Society for Biological and Environmental Repositories
LDH	Lactate dehydrogenase
LIMS	Laboratory information management system
LPO	Lead Protocol Organization
LV	LabVantage
MDS	Myelodysplastic Syndromes
MIOMS	Moffitt Immuno-Oncology and Molecular Services
miRNA	Micro RNA
MPN	Myeloproliferative Neoplasms
NCI	National Cancer Institute
NCORP	NCI Community Oncology Research Program
NCTN	National Clinical Trials Network
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OMB	Office of Management and Budget
OPEN	Oncology Patient Enrollment Network
OSMB	Observational Study Monitoring Board
PA	Physician Assistant
PBMCs	Peripheral blood mononuclear cells
PC	Project coordinator
PI	Principal Investigator
PNH	Paroxysmal Nocturnal Hemoglobinuria
PROMIS	Patient Reported Outcomes Measurement Information System
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
QUALMS	Quality of Life in Myelodysplasia Scale
RBC	Red blood cell
RIN	RNA integrity number
RN	Registered Nurse
RNA	Ribonucleic Acid
RSS	Regulatory Support System
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
T&UM	Transfer and Update Module
TC	Tissue Core
TCR	T cell receptor
TC-RSH	Tissue Core Histology Services
TC-SPL	Tissue Core Sample Processing Lab
TIBC	Total iron-binding capacity
TORFP	Task Order Request for Proposal
TSH	Thyroid-Stimulating Hormone
VES-13	Vulnerable Elders Survey
W/G	Wright-Giemsa
WHO	World Health Organization

1.0 INTRODUCTION

The National Myelodysplastic Syndromes Natural History Study (The National MDS Study) is a prospective cohort study to establish a publicly available resource to facilitate the understanding of the natural history of MDS. This study will enroll participants who are suspected of having MDS (including MDS/MPN overlap) or who are within 12 months of diagnosis and untreated, from centers in the National Cancer Institute (NCI) National Clinical Trials Network (NCTN) and the NCI Community Oncology Research Program (NCORP). Participants with newly diagnosed and untreated MDS, MDS/MPN, or AML with < 30 % blasts without core binding factor or acute promyelocytic leukemia (APL) [AML < 30% blasts including chromosomal rearrangements between chromosomes 8 and 21 and within chromosomes 16 as well as t(15;17)], or idiopathic cytopenia of undetermined significance (ICUS), identified by a centralized pathology review will be assigned to the longitudinal cohort study and followed prospectively every six months for disease progression. No more than 3500 participants will be registered.

Study participants with MDS, MDS/Myeloproliferative Neoplasms (MPN), AML with < 30% blasts without core binding factor or APL, and ICUS may be followed for life. Biological specimens, clinical data, and Quality of Life (QOL) assessments are requested during follow-up. The specimens and data will be linked and stored for future research studies.

Adequate understanding of MDS natural history is required to improve MDS diagnosis, classification and prognosis, inform medical decision making for MDS patients, facilitate biomarker discovery, define the optimal use of existing therapies, identify new therapeutic targets and inform efforts to understand disease etiology and prevention. This understanding necessarily involves the detailed description of genetic and epigenetic changes.

A biospecimen repository that supports this type of systematic inquiry must include consistently processed biospecimens annotated with high-quality clinical data, and the collection of biospecimens must be large to encompass the broad heterogeneity of MDS and allow evaluation of the biology of specific subtypes with reasonable statistical power. Specimens from an appropriate group of participants with ICUS may allow delineation of molecular or other factors uniquely associated with MDS-related cytopenias.

Furthermore, the collection of QOL data will provide an opportunity to study the health outcomes of patients with MDS as it is affected by treatments and disease progression, and in comparison, to healthy adults and other patients with neoplasms.

The National MDS Study will address these needs through a multi-center initiative to uniformly collect and store high quality biological specimens and clinical data from a large, prospective cohort of participants suspected of having MDS. This resource will be made available to the biomedical community and is expected to facilitate the next generation of high-impact research studies in MDS.

1.1 Study Websites

General information about the study is available on the public website at https://thenationalmdsstudy.net/. At this website, the public can view information about MDS, the

study sponsor and collaborators, participating clinical centers, and study-related links. A notable feature of the public website is the clinical center search function. Potential study participants can search the map and center listing by state to find the closest participating sites.

In addition, staff at clinical centers can view study-related links on the Study Information tab, including a link to the ECOG-ACRIN Cancer Research Group website where the protocol is posted. Please note, detailed study information, study materials, and regulatory requirements to register as a participating center are available to NCI National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) centers on the Cancer Trials Support Unit (CTSU) website (https://www.ctsu.org/).

A private website (requiring a username and password) is also accessible at https://thenationalmdsstudy.net/. The Protocol Team, Steering Committee, and study team members at the NHLBI, NCI, Data Coordinating Center (DCC), and Central Laboratory/Biorepository (CL/B) can use the private website to view password-protected administrative documents such as meeting agendas and minutes as well as web reports for accrual, demographics, data quality, lab compliance, safety reporting, and other study data.

The 'MDS Interactive Inventory Browser' is a dynamic publicly accessible database query tool that allows one to identify cohorts of interest from our study and perform research feasibility analysis based on the availability of clinical, lab, and genetic data. The browser is maintained on the public website https://thenationalmdsstudy.net/ but requires a login account to access. Any individual can complete and submit a "Registration Form" to obtain access to the browser.

The DCC maintains the public and private websites accessible at https://thenationalmdsstudy.net/. Any questions, including requests for access to the private website, should be directed to the DCC. Questions regarding the information on the CTSU website should be directed to the appropriate contact at the CTSU. See Appendix VII for contact information.

2.0 STUDY ORGANIZATION

2.1 Study Objectives and Organizational Overview

The objective of The National MDS Study is to establish a publicly available resource to facilitate the study of the MDS disease process. The study will create a multi-institutional, longitudinal biorepository of consistently processed and clinically well-annotated blood and tissue specimens, collected prospectively from a longitudinal cohort of up to 2000 participants with newly diagnosed and untreated MDS, and will continue to follow all participants in the longitudinal cohort at six month intervals during this period. The study will also support investigator-initiated studies of MDS that will have a high impact for MDS participants, including basic science, clinical and epidemiological research.

The study is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the National Cancer Institute (NCI). Under the direction of the NHLBI, the study is conducted via the leadership of the appointed Protocol Team and Steering Committee and with resources committed to a contracted DCC and a CL/B.

2.2 National Institutes of Health (NIH) Program Offices

2.2.1 National Heart, Lung, and Blood Institute (NHLBI)

This project has been funded using Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contracts No. HHSN268201400002I and HHSN268201400003I. The Contracting Officer's Representatives (COR) are located in the NHLBI's Division of Blood Diseases and Resources (DBDR). The COR is responsible for: (1) monitoring the Contractor's technical progress, including the surveillance and assessment of performance and recommending to the Contracting Officer changes in requirements; (2) interpreting the statement of work and any other technical performance requirements; (3) performing technical evaluation as required; (4) performing technical inspections and acceptances required by this contract; and (5) assisting in the resolution of technical problems encountered during performance.

Other NHLBI team members include members of NHLBI's Office of Biostatistics Research, and a Contracting Officer and a Contracting Specialist from the Office of Acquisitions. The Contracting Officer is the only person with authority to act as agent of the Government under this contract. Only the Contracting Officer has authority to: (1) direct or negotiate any changes in the statement of work; (2) modify or extend the period of performance; (3) change the delivery schedule; (4) authorize reimbursement to the Contractor for any costs incurred during the performance of this contract; (5) otherwise change any terms and conditions of this contract; or (6) sign written licensing agreements.

2.2.2 National Cancer Institute (NCI)

Members of the NCI Division of Cancer Prevention (DCP) and Cancer Therapy Evaluation Program (CTEP) assist in the development and implementation of the protocol. Resources from the NCI research program are used to identify centers, recruit participants and acquire clinical data.

NCI supports clinical sites that are members of the NCI NCTN and NCORP programs. NCI also reviewed and approved the protocol, and supported CIRB review.

2.3 Technical Committees

2.3.1 Protocol Team

The Protocol Team consists of a Chair and additional members appointed by the NHLBI. This Protocol Team has a responsibility to develop and finalize the protocol for the study, to advise the institute on policy issues such as specimen and data sharing during the conduct of the study and to identify and resolve obstacles to study conduct. The Protocol Team includes representatives from the adult clinical groups in the NCTN and NCORP, as well other experts. The Protocol Team also provides scientific leadership and operational guidance for the study. All members including the DCC Principal Investigator (PI) and the Central Laboratory/Biorepository (CL/B) PI are voting members. During protocol development, the team met two times per year in-person in Bethesda, Maryland, and attended up to six teleconferences per year. The Protocol Team members are:

- Mikkael Sekeres, MD, MS (Chair), Sylvester Cancer Center, University of Miami, Don Soffer Clinical Research Bldg, Div. of Hematology
- Amy DeZern, MD, MHS, (Deputy Chair), Johns Hopkins University
- Steven Gore, MD, (Deputy Chair), Cancer Therapy Evaluation Program NIH/NCI
- Gregory Abel, MD, MPH, (Quality of Life Chair) Dana-Farber Cancer Institute
- Tareq Al Baghdadi, MD, IHA Hematology Oncology Associates
- Rafael Bejar, MD, PhD, University of California, San Diego (UCSD) Moores Cancer Center
- James Cerhan, MD, PhD, Department of Health Sciences Research, Mayo Clinic
- Joachim Deeg, MD, Fred Hutchinson Cancer Research Center
- Nancy Gillis PharmD, PhD (CL/B Co-PI), Moffitt Cancer Center
- Eric Padron, MD (CL/B Co-PI), Moffitt Cancer Center
- Edward J. Gorak, III, DO, MS, Geisinger Medical Center
- Jane Liu, MD, Illinois CancerCare, P.C.
- Michael Otterstatter, PhD (DCC Co-PI and Study Statistician), The Emmes Company
- Seth Sherman, PhD (DCC Co-PI), The Emmes Company
- Daniel Starczynowski, PhD, Cincinnati Children's Hospital Medical Center
- Matthew Walter, MD, Washington University School of Medicine

Protocol Team Technical Advisor

- Ben Ebert, MD, Brigham and Women's Hospital

2.3.2 Steering Committee

The Steering Committee consists of a subset of the Protocol Team, including the Protocol Chair, and additional members appointed by the NHLBI. The Steering Committee includes representatives from the adult clinical groups in the NCTN and NCORP, as well other experts. The

committee advises the institute on policy issues, identifies obstacles to study conduct, and provides scientific leadership and operational guidance. All members including the DCC Principal Investigator (PI) and the Central Laboratory/Biorepository (CL/B) PI are voting members. The Steering Committee meets two times per year in-person and attends ad hoc teleconferences.

The Steering Committee members are:

- Mikkael Sekeres, MD, MS (Chair), Sylvester Cancer Center, University of Miami, Don Soffer Clinical Research Bldg, Div. of Hematology
- Amy DeZern, MD, MHS, (Deputy Chair), Johns Hopkins University
- Steven Gore, MD, Cancer Therapy Evaluation Program NIH/NCI
- Gregory Abel, MD, MPH, (Quality of Life Chair) Dana-Farber Cancer Institute
- Tareq Al Baghdadi, MD, IHA Hematology Oncology Associates
- Rafael Bejar, MD, PhD, University of California, San Diego (UCSD) Moores Cancer Center
- Joachim Deeg, MD, Fred Hutchinson Cancer Research Center
- Nancy Gillis PharmD, PhD (CL/B Co-PI), Moffitt Cancer Center
- Eric Padron, MD (CL/B Co-PI), Moffitt Cancer Center
- James Foran, MD, Mayo Clinic
- Edward J. Gorak, III, DO, MS, Geisinger Medical Center
- Rami Komrokji, MD, Moffitt Cancer Center
- Jane Liu, MD, Illinois CancerCare, P.C.
- Michael Otterstatter, PhD (DCC Co-PI and Study Statistician), The Emmes Company
- Seth Sherman, PhD (DCC Co-PI), The Emmes Company
- Daniel Starczynowski, PhD, Cincinnati Children's Hospital Medical Center
- Matthew Walter, MD, Washington University School of Medicine

Steering Committee Technical Advisor

- Ben Ebert, MD, Brigham and Women's Hospital

2.3.3 Subcommittees

The members of the Protocol Team and Steering Committee participate collaboratively and may be active participants in one or more subcommittees. The DCC and the CL/B participate in all subcommittees. The subcommittees include a standing Publications Committee. Other subcommittees (e.g. QOL subcommittee or Histopathology subcommittee) are formed to meet the needs of the study as requested by the study leadership and meet as needed during the study. Subcommittee Chairs are selected by the Steering Committee and the NHLBI, and members may be selected from investigators at clinical sites participating in the study, or experts appointed by the NHLBI. Subcommittee Chairs report subcommittee activities to the full Steering Committee. The subcommittees make recommendations to the Steering Committee and the NHLBI. NHLBI will make final approval of recommendations.

The Steering Committee and subcommittees will communicate with investigators via the web, email, and teleconference. Investigators will also be engaged at group meetings in appropriate sessions such as leukemia committee meetings, general education sessions, or QOL-focused sessions. Group meeting presentations on the study will be coordinated by the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN).

Quality of Life (QOL) Subcommittee

- Gregory Abel, MD, MPH, (Protocol Team and Steering Committee Quality of Life Chair) Dana-Farber Cancer Institute
- Mikkael Sekeres, MD (Protocol Team and Steering Committee Chair), Sylvester Cancer Center, University of Miami, Don Soffer Clinical Research Bldg, Div. of Hematology
- David Cella, PhD, Northwestern University
- James Cerhan, MD, PhD, Department of Health Sciences Research, Mayo Clinic
- Paul B. Jacobsen, MD, University of South Florida

The QOL Subcommittee met via teleconference on an ad hoc basis to develop the quality of life component of the protocol. The subcommittee recommended the QOL instruments and submission schedule for the study taking into account the usefulness of the assessments and participant response burden.

Histopathology Subcommittee

- John M. Bennett, MD, University of Rochester Medical Center
- Alexandra Harrington, MD, Medical College of Wisconsin
- Steven Kroft, MD, Medical College of Wisconsin
- Lynn Moscinski, MD, Moffitt Cancer Center
- Ling Zhang, MD, Moffitt Cancer Center

The Histopathology Subcommittee met via teleconference to develop the pathology review processes in the protocol. The subcommittee defined the materials needed for the pathology review, reviewed pathology data forms, and assisted in development of the Central Pathology Review process.

Genetics Subcommittee

- Ben Ebert, MD, Brigham and Women's Hospital (Chair)
- Rafael Bejar, MD, PhD, University of California, San Diego (UCSD) Moores Cancer Center
- Steven Gore, MD, Cancer Therapy Evaluation Program NIH/NCI
- R. Coleman Lindsley, MD, PhD, Dana-Farber Cancer Institute
- Jaroslaw Maciejewski, MD, PhD, Cleveland Clinic
- Eric Padron, MD, Moffitt Cancer Center
- Matthew Walter, MD, Washington University School of Medicine

The Genetics Subcommittee meets via teleconference to discuss research to enhance the study resource. The committee discusses the value and practical considerations associated with genetics analysis such as the use of whole genome sequencing, whole exome sequencing, and/or targeted sequencing approaches. Other details including sequencing depth, factors affecting site selection for assay performance, sample requirements, and the need to maintain sufficient specimens for future research are considered. The committee reports recommendations to the Steering Committee and will meet via teleconference as needed to discuss additional recommendations during the study.

2.3.4 Observational Study Monitoring Board (OSMB)

The members of the OSMB are appointed by the NHLBI and act as an independent advisory group that provides recommendations regarding starting, continuing, and stopping the study to the NHLBI. The OSMB is also responsible for reviewing the study protocol, informed consent template, and OSMB reporting templates before the study can start enrollment. All protocol modifications and any ancillary studies that require additional contact with study participants will be reviewed by the Board. The OSMB will meet up to two times per year via teleconference.

The OSMB includes experts in the following areas: MDS and leukemia, histopathology, ethics, participant advocacy, and statistics, cohort studies and biorepositories. Conflicts of Interest (COI) for board members will be reviewed and managed. Generally, the OSMB members will be appointed to their positions for the duration of the study or contract award. Ad hoc members can also be appointed to the OSMB if needed. The OSMB activities are conducted per the NHLBI policies available at the following link: http://www.nhlbi.nih.gov/research/funding/human-subjects/data-safety-monitoring-policy.

2.3.5 Executive Committee

The Executive Committee (EC) oversees the day-to-day operations of the study as an extension of the Protocol Team and Steering Committee to ensure efficient and quality performance. The EC includes the Protocol Team and Steering Committee Chair, the PI of the DCC, the PI of the CL/B, the NHLBI CORs, an NCI Program Administrator, and the NHLBI Contracting Office representatives. This group meets monthly via teleconference. Recommendations made by the EC are presented to the full Steering Committee for approval. Final approval for all recommendations from the EC will be made by the study sponsor.

2.4 Data Coordinating Center (DCC)

2.4.1 The Emmes Company

The DCC activities are executed by Emmes under contract to the NHLBI. Emmes is responsible for coordinating and subcontracting scientific services needed for the study, such as a centralized multi-reader histopathology review, and protocol-defined research studies to enrich the study data set. Emmes aggregates, stores, and analyzes data collected at clinical sites and research laboratories. Emmes is responsible for transferring data files and summary reports to investigators, the OSMB, and the NHLBI throughout the study. The DCC is also responsible for creating databases and public use data sets, maintaining participant confidentiality, and creating and

maintaining public and private web sites, as well as coordinating and supporting all meetings and teleconferences of the committees and subcommittees for this study.

2.4.2 ECOG-ACRIN Cancer Research Group

Emmes has subcontracted with the NCI-funded ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) to identify clinical sites and capture clinical data for the study following NCI standards. ECOG-ACRIN staff have a central role in guiding the protocol through the protocol review process, site initiation, data capture and data quality review.

ECOG-ACRIN will sponsor the interface for all network groups and NCORP sites. ECOG-ACRIN will not restrict participation in this study, and it will be open to network groups and NCORP sites through Cancer Trials Support Unit (CTSU).

2.4.3 Consultants and Histopathologists

The study team identified Dr. Steven Kroft, MD, and Dr. Alexandra Harrington, MD, of the Medical College of Wisconsin as medical and histopathology consultants to assist in protocol development and the centralized review of bone marrow biopsies and aspirates. Dr. Kroft and Dr. Harrington will be the external pathologists for the study as described in section 9 Central Pathology Review for Study Assignment.

2.4.4 Role of the DCC

The DCC assisted with the development of the study protocol and is responsible for the overall coordination and management of the study, operational and analytical methodology, providing support to the research studies necessary to enrich the value of the resource developed, monitoring the clinical sites, and study data management. The DCC collaborates with the CL/B to develop and validate an IT interface to electronically transfer the biospecimen inventory and assay data to the DCC for inclusion in the study data set, and can conduct robust informative searches of the inventory. The DCC retrieves, stores, and analyzes study data, provides study reports, and provides any data collection and analysis software necessary for the success of the study.

2.5 Central Laboratory/Biorepository (CL/B)

2.5.1 Moffitt and MIOMS

Moffitt consists of The Cancer Center, a not-for-profit corporation, located in Tampa. The CL/B, which is physically located at the Moffitt Immuno-Oncology and Molecular Services Building (MIOMS) will ensure that samples are properly collected, processed, annotated, stored, and distributed to researchers through an independent contract with the NHLBI. All processes will be conducted using guidelines from the National Cancer Institute (NCI) Best Practices for Biospecimen Resources (https://biospecimens.cancer.gov/bestpractices/). Moffitt Cancer Center has successfully attained the College of American Pathologists (CAP) Biorepository Accreditation which is based largely on evidence-based collection of NCI Best Practices and International Society for Biological and Environmental Repositories (ISBER) best practices. Additionally, the CL/B is staffed with dedicated personnel who are all International Air Transport

Association (IATA) certified for shipping of hazardous materials by air freight. Central Pathology Review (CPR) will be conducted by Lynn Moscinski, MD and Ling Zhang, MD. Both are board certified hematopathologists with extensive expertise in MDS diagnosis and classification.

2.5.2 Role of the CL/B

The CL/B assists in development of the study protocol and collaborates with the DCC and clinical sites to implement the protocol.

Specifically, the CL/B is responsible for the following:

- Provide Standard Operating Procedures for biospecimen collection, shipping, processing, analysis, storage, and distribution to researchers.
- Perform assays as specified in section 8.5.5 Quality Assurance/Quality Control.
- Use Standard Operating Procedures (SOPs) for specimen shipping and distribution, receipt, processing, analysis, and storage.
- Provide a biospecimen inventory consisting of frozen bone marrow mononuclear cells (BM-MNCs), bone marrow plasma, frozen peripheral blood mononuclear cells (PBMCs), serum from peripheral blood, DNA and RNA from BM-MNCs, PBMCs, and purified CD34+ cells from bone marrow and T-cells from peripheral blood.
- Provide histopathology and technical expertise.
- Electronically transfer the biorepository data to the DCC.
- Perform assays as defined in the Task Order Request for Proposal (TORFP).
- Define methods to securely transfer de-identified samples to the NHLBI for long-term storage.

2.6 Clinical Centers

Clinical sites enrolling participants in the study are members of the NCTN or the NCORP. The clinical sites are responsible for recruitment of participants, enrollment and follow-up visits as defined in the protocol, and timely collection and provision of biospecimens and clinical data to the DCC and the CL/B as specified by the protocol. The clinical sites use NCTN software programs for participant registration and electronic data capture and management. GlobalTrace℠ will be used for clinical sample shipment and tracking. See sections 5 Data Systems and Data Integration and 6 Site Training for details.

2.7 MDS Research Requests

The NHLBI MDS study invites researchers to request access to a rich clinical dataset, samples, digital H&E slides, and genetic sequencing data collected from MDS patients enrolled across the US. The Resource Request Portal is available to the public at: https://thenationalmdsstudy.net/mds-study-information. An interactive Inventory Browser allows investigators to assess the types of available data.

From the portal, basic, translational, and clinical scientists can request data and specimens to pursue cutting-edge research that will contribute to our understanding of MDS and improve diagnostic and treatment options. All requests for MDS resources are managed by the MDS Data Coordinating Center and should be submitted through the National MDS Natural History Study website, https://thenationalmdsstudy.net/. The process for requesting data and specimens involves a two-stage review (a feasibility assessment and a research proposal stage). The specific steps involved in each of the stages are defined on the publica website here: https://thenationalmdsstudy.net/content/request-workflow-guide.

3.0 PROTOCOL DEVELOPMENT, REVIEW, APPROVAL AND RELEASE

3.1 Developing the Protocol Team and Steering Committee

The NHLBI appointed the members of the Protocol Team and Steering Committee. The committees consist of representatives from the NCTN and NCORP as well as other experts in MDS clinical and translational research. The Protocol Team developed and finalized the protocol with the NHLBI, NCI, CL/B, and DCC. The approved protocol is submitted for scientific review through the NCI DCP process and the NHLBI OSMB.

3.2 Review of Protocol by the OSMB

The OSMB reviews and accepts the protocol prior to the start of the study. During the study, the OSMB will routinely meet and provide recommendations to the NHLBI regarding changes to the protocol and consent form related to human subjects' safety and ethics. Refer to section 2.3.3 for additional responsibilities of the OSMB.

3.3 Review by the NCI Division of Cancer Prevention (DCP) and the Cancer Prevention and Control (CPC) Central Institutional Review Board (CIRB)

Upon initial scientific review and approval by DCP, the protocol documents are routed to the CPC CIRB for review and approval prior to release to sites for accrual. ECOG-ACRIN will be responsible for coordinating responses to the DCP reviews and the CPC CIRB stipulations and comments.

CPC CIRB approval is required prior to activation and accrual. The study is reviewed annually for continued enrollment.

3.4 Release of Protocol to Participating Center

Upon final DCP protocol approval, ECOG-ACRIN will post the study materials on the ECOG-ACRIN webpage and the CTSU website. A group-wide broadcast will be released informing the NCTN and NCORP sites that the study is active. The CTSU will also include the activation in the CTSU bi-monthly broadcast to CTSU member sites (which includes all NCTN and NCORP sites).

3.5 Documentation of Initial and Continuing IRB Approval

3.5.1 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll participants. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

3.5.2 DCP CPC CIRB Approval

Sites participating on the NCI CIRB initiative and accepting CPC CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing, or amendment review. However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.6 Procedures for Protocol Amendments

Any changes identified and agreed upon by the NHLBI, Steering Committee, and the OSMB will be incorporated into the protocol by the DCC. The DCC will forward the changes, justification and summary of edits to ECOG-ACRIN for submission to DCP and CPC CIRB for approval.

ECOG-ACRIN will prepare the protocol documents in e-submission-compliant format and route to DCP for review and approval. ECOG-ACRIN will be responsible for responding to any stipulations or requests for additional information necessary to achieve approval.

3.7 Review of Protocol Amendments

All amendments will be reviewed and approved by DCP and CPC CIRB prior to release to sites.

3.8 Finalizing Protocol Amendments

Upon receiving DCP amendment approval, an activation date for the changes to become effective will be determined, and activation materials will be finalized for release to sites.

3.9 Case Report Form Revisions

Data management staff at ECOG-ACRIN will revise case report forms (CRFs) to correct errors and to accommodate protocol amendments. Data management staff will initiate a CRF revision in a study-specific change control document that is reviewed by the Manager of Study Setup.

The study builder at ECOG-ACRIN makes the requested changes in a project draft and circulates the CRFs to all reviewers. The reviewers include the study chair and co-chair, statistician, data manager (DM), project coordinator (PC) for disease site, Director of Data Management, and Manager of Study Setup.

All reviewers provide comments on the drafted form changes to the study builder, who incorporates the comments and makes additional forms revisions as needed. The study builder may organize a meeting among all reviewers to finalize forms changes, if necessary.

After the CRFs are approved, the data manager validates the changes in the study database.

The internal team (DM, PC of disease site, and Manager of Study Setup) schedules publishing of revised forms to the production database.

3.10 Certificate of Confidentiality

A certificate of confidentiality is issued for NIH studies performing genomics. ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS) to ensure the protection of participant privacy. With this Certificate, ECOG-ACRIN cannot be forced to disclose information that may identify the study participant in any federal, state or local civil, criminal, administrative, legislative or other proceeding. This and other details pertaining to medical information protection have been included in the consent form.

3.11 Data Use Agreement

Members of the study team may be provided access to individual case and/or study-wide results for the ongoing study. Data shall only be used for internal data monitoring purposes except for publications and presentations approved in accordance with procedures described in the Manual of Procedures. Anyone with access to non-public data will not release, publish, disclose or provide access to unauthorized individuals and shall protect such information from accidental or malicious release. Any unapproved use or release must be reported to the DCC and may jeopardize future access to study data.

4.0 CLINICAL CENTER PROCEDURES

4.1 Functions of the Principal Investigator

The principal investigator (PI) is ultimately responsible for all study-related activities at his/her institution. This includes activities such as data management, protocol compliance including specimen capture and submission, and other site investigators. The PI must ensure all staff at his/her site who will participate in the study have adequate training in all aspects of the study such as study conduct and data management, and that all have completed human subjects research protection training.

4.2 Functions of the Clinical Research Coordinator

Under the direction of the PI, the Clinical Research Coordinator is responsible for many tasks related to the day-to-day conduct of the study such as participant enrollment, scheduling, data management, protocol compliance, and similar tasks.

4.3 Site Registration and Activation

4.3.1 CTEP Investigator and Associate Registration Procedures via the Registration and Credentialing Repository (RCR)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Access is managed through the Cancer Therapy Evaluation Program - Identity and Access Management (CTEP-IAM) registration system. A valid user name and password from IAM is required for access to the CTSU website. Registration in the Registration and Credentialing Repository (RCR), a self-service online person registration application with electronic signature and document submission capability, is also necessary for most users. The RCR recognizes five types of registered users:

- Investigators (IVR) – licensed MD, DO, or equivalent.
- Non-Physician Investigators (NPIVR) - advanced practice clinical staff who may act as
- study principal investigators (PI), site-protocol PIs, or enrolling PIs in OPEN for select studies.
- Associate Plus (AP) – clinical site staff integral to the conduct of NCI-supported studies.
- Associate (A) – other clinical or administrative staff that require access to NCI-supported applications but act in a supporting role (ordering designees, regulatory submissions, etc.).
- Associate Basic (AB) – individuals that require limited access to select NCI-supported applications or are tracked for administrative purposes (i.e., industry contacts). ABs will not have access to the CTSU website.

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators (IVRs and NPIVRs) participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Investigator registration will be completed in the RCR and requires electronic submission of:

- FDA Form 1572
- Financial Disclosure Form
- NCI Biosketch
- Agent Shipment Form (if applicable)
- Human Subjects Protection
- Good Clinical Practices
- Optional Curriculum Vitae (CV)

APs must complete an annual registration in RCR and electronically submit a Financial Disclosure Form, NCI Biosketch, Human Subjects Protection, Good Clinical Practice, and Optional CV.

Associates and ABs will perform annual registration using IAM. Associates may access the CTSU website and systems including view access to OPEN and Rave. ABs may not access the CTSU website or systems.

4.3.2 Resources and Links to Webpages

To obtain or update IAM credentials, including the username and password necessary to log-in the CTSU website, visit the IAM registration page: https://ctepcore.nci.nih.gov/iam

To register in the RCR, visit: https://ctepcore.nci.nih.gov/rcr

For help with RCR, contact the RCR Helpdesk: RCRHelpDesk@nih.gov

4.3.3 Access to NCI Sponsored Systems for Trial Participation

Access to the CTSU members' website allows users at clinical institutions participating on NCI-supported trials to view several resources including:

- Protocol and protocol-related documents
- Funding information for studies under the NCI National Clinical Trials Network (NCTN)
- NCI Central Institutional Review Board (CIRB) documents for sites participating in the CIRB initiative
- Links to Medidata Rave® and the Oncology Patient Enrollment Network (OPEN)
- Access to the Data Quality Portal, Site Audit Portal, and accrual information
- Information on regulatory submissions
- Educational materials
- E-mail notification on protocol updates and CTSU-supported activities

4.3.4 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU). For additional information on the CTSU, visit https://www.ctsu.org.

4.3.5 IRB Approval

Refer to section 3.5 Documentation of Initial and Continuing IRB Approval.

4.3.6 Downloading Site Registration Documents

Site registration forms may be downloaded from the NHLBI-MDS protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the Lead Group = ECOG-ACRIN to expand, then select trial protocol #NHLBI-MDS
- Click on the Site Registration Documents link

4.3.7 Requirements for NHLBI-MDS Site Registration

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- Complete Protocol, Biospecimen Acquisition, Biospecimen Shipping, GlobalTrace, and Medidata Rave Training Modules (See Appendix II for site training materials). Site personnel must complete the training modules as noted below:
  - At least one investigator from each enrolling site must complete the Protocol and Biospecimen Acquisition training modules.

  AND
  - At least one coordinator from each enrolling site must complete all five training modules: Protocol, Biospecimen Acquisition, Biospecimen Shipping, GlobalTrace, and Medidata Rave.
- Complete and submit "The National MDS Study: Site Information Checklist" (Appendix III) to the CTSU Regulatory Office.
  - On the Site Information Checklist, the site must identify at least one staff member certified with International Air Transport Association (IATA) or equivalent training to ship biological substances and also submit their certificate with the Site Information Checklist to the CTSU Regulatory Office.
  - The CL/B reviewer may contact the site directly (with a copy to the CTSU and the DCC) to resolve questions or comments.

- **Final approval for the enrolling site will be submitted directly from the CL/B to the CTSU Regulatory Office and is required prior to first participant enrollment.**

Refer to Appendix I NHLBI-MDS Site Registration Process for additional details on the requirements for site registration and submission procedures.

4.3.8 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Institutions with participants waiting that are unable to use the portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.3.9 Required Protocol Specific Regulatory Documents

- Copy of IRB Informed Consent Document.

  NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

- CTSU IRB Certification Form **or** Signed Health and Human Services (HHS) Office of Management and Budget (OMB) No. 0990-0263 (replaces Form 310) **or** IRB Approval Letter

  NOTE: The above submissions must include the following details:
  - Indicate all sites approved for the protocol under an assurance number.
  - Office for Human Research Protections (OHRP) assurance number of reviewing IRB
  - Full protocol title and number
  - Version Date
  - Type of review (full board vs. expedited)
  - Date of review.
  - Signature of IRB official

4.3.10 Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website.

NOTE: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

4.3.11 Participant Enrollment

Refer to section 5.2 Oncology Patient Enrollment Network (OPEN).

4.3.12 Contact Information

Questions regarding CTEP Investigator Registration, Associate Registration, or CTEP-IAM Accounts should be directed to the Investigator Registration Help Desk and the Associate Registration Help Desk. Questions regarding Site Registration and OPEN should be directed to the CTSU Help Desk. See Appendix VII for contact information.

4.4 Recruitment and Compensation

Funding for enrolled cases depends on whether the individual is eligible for entry into the longitudinal cohort subsequent to Central Pathology Review and study assignment. NCTN (Non-NCORP) Institutions will receive federal funds through ECOG-ACRIN. NCORP institutions will receive credits with a single credit having a dollar equivalent of $2500.

All enrolled participants will receive the base payment of $1250 (.5 credit for NCORP Sites). For participants with MDS, MDS/MPN overlap disorders, or AML with < 30% blasts without core binding factor or APL (up to 2000 participants) plus At-Risk participants or those with ICUS (up to 500 participants) who proceed to the Longitudinal Study Cohort after Central Pathology Review, institutions receive an additional payment of $1250 (.5 credit for NCORP Sites). ECOG-ACRIN will be responsible for recording this payment in the OPEN funding screen.

4.5 Eligibility Criteria

- Suspected (e.g., persistent unexplained cytopenia, circulating peripheral blasts etc.) MDS or MDS/MPN overlap disorders and undergoing diagnostic work-up with planned bone marrow assessments **OR**
- Diagnosed with *de novo* or therapy-related MDS within 12-months of enrollment per the World Health Organization (WHO) criteria and undergoing clinical evaluation and planned bone marrow assessments to confirm MDS or to evaluate disease status

- Bone marrow aspirate expected to be performed within 1 week of registration, and in all cases must be performed no later than 4 weeks after enrollment
- Age 18 or older
- No prior treatment for MDS at entry and through the time of the entry bone marrow aspirate
- No treatment with hematopoietic growth factors in prior 6 months
- If anemic without prior MDS diagnosis, the following tests within the prior 6 months. Values that are significantly outside of normal range do not exclude participation but should prompt investigation of alternative etiologies for anemia.
  - B12 level
  - Serum folate
  - Mean corpuscular volume (MCV)
  - Red cell distribution width (RDW)
  - Ferritin
  - Iron studies (Iron, Total Iron-Binding Capacity (TIBC) Test, Percent Saturation)
- No diagnosis of a solid tumor or hematologic malignancy within two years prior to enrollment except for in situ cancer of the skin (basal or squamous cell), cervix, bladder, breast, or prostate
- No treatment with radiation therapy in the two years prior to registration
- No non-hormonal treatment for malignancy within the two years prior to registration
- No established hereditary bone marrow failure syndrome
- No known *primary* diagnosis of aplastic anemia, classical paroxysmal nocturnal hemoglobinuria, amegakaryocytic thrombocytopenic purpura, or large granular lymphocyte leukemia
- Not enrolled in the Connect® MDS/AML Disease Registry

Based on centralized pathology review, participants will be classified into the longitudinal cohort of cases (MDS, MDS/MPN overlap disorders, AML with < 30% blasts without core binding factor or acute promyelocytic leukemia [AML < 30% blasts including chromosomal rearrangements between chromosomes 8 and 21 and within chromosome 16 as well as t(15;17)], ICUS, or at risk based on selected genetic markers) and the cross-sectional cohort (all others). It is not known in advance what percentages of individuals will fall into each cohort. In addition to baseline biological samples, longitudinal samples and data will be collected for up to 2000 participants with MDS, MDS/MPN overlap disorders, or AML, and 500 Cases of ICUS assigned to the longitudinal cohort. Sample and data collection will cease at baseline for all cases assigned to the cross-sectional cohort.

Submitted pathology slides will be reviewed by the Central Hematopathologists to determine eligibility for the longitudinal cohort (i.e., an MDS, MDS/MPN, AML with < 30% blasts without core binding factor or APL, or ICUS diagnosis). Should a discrepancy in diagnosis occur between the blinded Central Pathology Review and study site, the Central Hematopathologist will first gain access to the pathology report generated from the study site. If the difference in diagnosis/classification cannot be adjudicated, then the diagnostic slides will be sent to an

additional study histopathologist for review. If there is a change in the participant's classification or eligibility based on these reviews, then the study site will be notified. Such notifications will not occur in real time; clinical diagnosis and care remain in the purview of the treating institution's care providers.

4.5.1 Re-screening Subjects

Subjects that are not entered in the longitudinal study are eligible to be re-screened for participation in this study if progression of signs or symptoms provides evidence to support a probable diagnosis of MDS, MDS/MPN overlap disorders or ICUS.

A site should utilize the same participant ID number for this re-screen enrollment. Specimens for re-screen baseline visits should be entered into GlobalTrace with the Visit Number assignment **01S**. All other enrollment procedures, baseline criteria, expectations for specimen and data collection will remain the same.

For additional questions on eligibility or re-screening, contact the Study Chair Liaison at the DCC. Please notify the DCC when planning to re-screen a participant. See Appendix VII for contact information.

4.6 Obtaining Informed Consent

Study participants must not be registered prior to obtaining a signed and dated consent document.

4.6.1 Informed Consent Template

A model Informed Consent Document has been drafted and is available on both the ECOG-ACRIN and CTSU websites.

4.7 Transferring Study Participants

If a study participant informs a site that s/he needs to move to another site, the following actions occur:

1. The transferring site user utilizes the Transfer and Update Module (T&UM) (https://www.ctsu.org/OPEN_SYSTEM/) to find potential Receiving Sites.
2. The transferring site user confirms with the participant that the potential Receiving Site is agreeable or finds an alternative.
3. The transferring site user reaches an unofficial agreement with the Receiving Site that the transfer can occur.
4. The transferring site user initiates a Site Transfer request in the T&UM tab of OPEN.
5. A T&UM ID is generated. Receiving Site users are notified by email that the request is pending their review.
6. A Receiving Site user reviews the request in the T&UM tab of OPEN and makes a decision to accept or reject the request.
7. If accepted, an email is sent to all parties informing them that the request was accepted.

8. If rejected, an email is sent to all parties informing them that the request was rejected, and no update will be made.
9. Data updates for accepted request will be automatically performed in OPEN and the Lead Protocol Organization (LPO) database. The link between the participant ID and study is maintained in OPEN during the transfer process. Rave will be manually updated by LPO.

For additional questions, contact the CTSU Help Desk. See Appendix VII for contact information.

5.0 DATA SYSTEMS AND DATA INTEGRATION

5.1 Overview of the Data Management Architecture

This study will utilize three data systems described in detail in sections 5.2-5.4. Oncology Patient Enrollment Network (OPEN) will be utilized for enrollment. OPEN will initialize participants in Medidata Rave. Electronic data capture will be performed in Medidata Rave, and specimen shipments will be tracked in GlobalTrace.

The DCC, ECOG-ACRIN, and the CL/B will maintain the study database through secure data transfers between the data systems which will occur at least weekly but as often as daily or in real time when necessary for efficient function. Refer to Appendix V for the comprehensive Data Interchange Strategy.

Data system training is required for participating sites and will be conducted via online training modules. Refer to Section 6 Site Training for details.

Questions regarding OPEN should be directed to the CTSU Help Desk. Questions regarding CTEP-IAM Accounts should be directed to the Investigator Registration Help Desk or the Associate Registration Help Desk. Questions regarding Medidata Rave should be directed to the Data Manager at ECOG-ACRIN, and questions regarding GlobalTrace should be sent to the Study Chair Liaison at the DCC. See Appendix VII for contact information.

5.2 Oncology Patient Enrollment Network (OPEN)

Study participant enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam/index.jsp>) and a 'Registrar' role on either the Lead Protocol Organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll participants to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the participant in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol-stated time frames.
- All participants have signed an appropriate consent form and HIPAA authorization form (if applicable). NOTE: The OPEN system will provide the site with a printable confirmation of segment registrations. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The following documents must be on file at the CTSU Regulatory Office/Coalition of National Cancer Cooperative Groups before any institution may enter a study participant.

- Copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent
- One of the following:
  - CTSU IRB Certification Form OR
  - Signed HHS OMB No. 0990-0263 (replaces Form 310) OR
  - IRB Approval Letter

The investigator will register study participants via the OPEN Registration System, 24 hours a day, 7 days a week (https://open.ctsu.org). Near real time transfer of registration occurrences is made to ECOG-ACRIN and Emmes.

Questions regarding OPEN should be directed to the CTSU Help Desk. Questions regarding CTEP-IAM Accounts should be directed to the Investigator Registration Help Desk or the Associate Registration Help Desk. See Appendix VII for contact information.

5.3 Medidata Rave®

Electronic data capture will be conducted exclusively in Medidata Rave. Rave is a web-based remote data entry system. Access to Rave requires only a web browser and internet connection. There will be no paper case report forms submitted to the ECOG-ACRIN Operations Office – Boston. Data will be entered directly into Rave at the site by the clinical research associates (CRAs.) Central Office data management will be performed in Rave by the ECOG-ACRIN data management team. The data management team will routinely review the Rave eCRFs for discrepancies and missing data. Queries on discrepant or overdue data will be generated within Rave. There will be two types of queries: 1) pre-programmed site from system queries and 2) manual site from DM queries. CRAs can access and respond to these queries in the Rave database. For further information on data collection in Rave, please review the Introduction to Medidata Rave training slides.

Access to the NHLBI-MDS study in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS after IRB approval is obtained. To access iMedidata/Rave, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA, Read-Only, Site Investigator) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites.

The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website. The first time your site receives approval for a Rave study, you will automatically receive an iMedidata Invitation email. This is a one-time email that is generated when you are linked to your first study in iMedidata.

After your initial account creation is completed, you will receive a study invitation email for each subsequent Rave study to which your site registers. This study invitation email is sent at the time your site status is set to 'approved' for the study in the RSS and is associated with the study in iMedidata. For more detailed information, please log on to the CTSU website, www.ctsu.org, and click on the "Rave tab".

The activation email provides the new Rave user with a unique link to activate his/her account in iMedidata (iMedidata is a system that provides access to all authorized studies). The user will not be able to access the Rave system without completing this activation process. The activation email will expire 30 days after receipt. Once the account is activated, the user will receive a study invitation email to all subsequent Rave studies for which their site receives approval.

Once a user receives his/her study activation email and logs in to Rave, s/he will be assigned eLearnings (i.e., online training modules). Please see the Training section below for details.

Questions regarding Medidata Rave should be directed to the Data Manager at ECOG-ACRIN. See Appendix VII for contact information.

5.3.1 Follow-Up Procedures in Medidata Rave and OPEN

An automated email from ECOG-ACRIN will be sent to the sites when a participant has been assigned to a cohort for long term follow-up (longitudinal cohort) or collection of only the baseline samples and data (cross-sectional cohort). This information will be available after the Central Pathology Review is completed (see section 9 for details). After receiving the email notification, site staff must log into Medidata Rave to complete the Cohort Assignment form. For participants in the longitudinal cohort, completion of this form will open folders for subsequent study visits.

In addition, site staff must enter the Longitudinal Study Cohort date in OPEN to receive the $1250 conditional payment.

5.4 Advantage eClinical/GlobalTrace℠

The A**dvantage** eClinical/GlobalTrace℠ System is a secure web-based materials management application designed for specimen tracking in multi-center studies. GlobalTrace provides the clinical centers with an online environment for documenting and tracking information regarding the collection, inventory, and shipment of specimens to the CL/B. For best performance, Chrome 44 or higher, Firefox 40 or higher, EDGE, or Internet Explorer 9 or higher should be used to access Advantage eClinical. In addition, Safari 8 or higher may be used if you are accessing Advantage eClinical on a Mac. A user guide is available on the website and is also posted on CTSU.

Advantage eClinical is accessible at https://emmes.okta.com/login/login.htm .

This study will use unique specimen collection kit barcode labels to improve the reliability of the specimen inventories. Quality control procedures as described below will ensure validation of shipment contents and provide a mechanism to resolve discrepancies between the physical and electronic inventories.

The quality control mechanism will function as follows:

1. Pre-labeled specimen collection kits, including pre-labeled blood and bone marrow tubes, buccal swabs, and slide boxes for pathology slides and core biopsy slides, will be shipped to sites from the CL/B upon site activation and as needed during the study. Shipping materials will be provided with shipping instructions.
2. After collection of specimens from enrolled participants and prior to shipment to the CL/B, the barcode label on each specimen collection kit must be scanned (or manually entered) to populate the associated specimen ID numbers in the GlobalTrace system. The pathology and core biopsy slide boxes (not the individual slides) will also be scanned prior to shipment. Barcode scanners are available to sites upon request from the CL/B. Refer to Section 8.1.1 Labeling System for details.
3. A Shipping Manifest will be created in GlobalTrace after scanning the kits contained in the shipment and entering the specimen information. The manifest must be printed and included in the sample shipment to the CL/B. An automated email notification will inform the CL/B a shipment has occurred.
4. The shipment will be received at the CL/B where it will be accepted or rejected in GlobalTrace, and any discrepancies will be resolved.
5. NOTE: Sample tracking for this project is at the **Specimen Collection Kit** level. Therefore, it is imperative that when samples are collected, they are placed back into their respective **Specimen Collection Kit** and the barcode on the **collection kit** is scanned into GlobalTrace. DO NOT scan each sample collection tube into the system.

Note: Questions regarding GlobalTrace should be sent to the contact at the DCC. Questions regarding specimen shipments should be sent to the Clinical Coordinator at the CL/B. See Appendix VII for contact information.

5.4.1 Accepted Shipments

The CL/B will accept shipments in GlobalTrace when the contents of the physical shipment match the information entered in GlobalTrace at the site. If the following issues are identified, the CL/B will accept the shipments if the kit and specimen information has been entered accurately in GlobalTrace.

- If samples less than the requested quantity are received, the shipment will be accepted and the available samples will be processed.
- If there is a delay from time of sample acquisition to receipt at the CL/B greater than 48 hours, the shipment will be accepted in GlobalTrace. The samples will be processed, and the delay will be noted in LabVantage. The CL/B will follow up with sites if there are repeated delays in shipment.
- If any samples cannot be used, they will be destroyed at the CL/B.

5.4.2 Rejected Shipments- Discrepancy Between Physical and Electronic Shipments

Kits can be rejected in GlobalTrace for the following reasons: Incorrect data, Missing Required Samples(s), Wrong Kit, and Damaged Sample(s). **If the shipment is rejected, the samples will remain at the CL/B and site staff will need to update the shipment information electronically in GlobalTrace to match the specimens in the inventory as noted below.**

- Incorrect data: If the CL/B notices a discrepancy in the collection data entered for a kit (e.g. Visit Number, Participant ID, collection date), the CL/B will keep the samples and reject the shipment so the site can update/confirm the data before resending the electronic shipment back to the CL/B. The specimen collection information entered into GlobalTrace must accurately reflect the collection information of the physicial samples received at the CL/B.
- Missing Required Sample(s): If required samples are missing and the containers were noted as used in GlobalTrace, the CL/B will keep the samples received and electronically reject the shipment. The site will view the rejected shipment and update the sample information by entering that the containers for the missing samples were not used and noting the reason the samples were not sent in the comments field. The updated shipment must be electronically sent to the CL/B. The CL/B staff will review the information entered in GlobalTrace, and if correct, accept the shipment. The specimen information entered in GlobalTrace must match the actual samples received at the CL/B. If the missing sample is collected separately at the site, the kit should be entered in GlobalTrace and sent in a new shipment.
- Wrong Kit: If the sample collection kit number received at the CL/B does not match the sample collection kit number sent electronically, the CL/B will keep the samples and electronically reject the shipment. When a shipment has been rejected, the site will access GlobalTrace to delete the shipment, enter the correct information, and electronically send the information to be accepted at the CL/B. The specimen information entered into GlobalTrace must match the samples received at the CL/B.
- Damaged Sample(s): If a sample is damaged in transit and not usable when received at the CL/B, the CL/B will keep the samples and electronically reject the shipment. The site must view the rejected shipment and update the sample information in GlobalTrace to indicate the damaged container was not used. The site must send the electronic shipment back to the CL/B to be accepted. The specimen information entered into GlobalTrace must match the samples successfully received at the CL/B.

Questions regarding the GlobalTrace System should be sent to the contact at the DCC. Questions regarding specimen shipments should be sent to the Clinical Coordinator at the CL/B. See Appendix VII for contact information.

6.0 SITE TRAINING

Required training will be available through the web-based platform Mindflash. A link to the training will be available on the CTSU website with the study information (www.ctsu.org). The training includes the following modules: Protocol, Biospecimen Acquisition, Biospecimen Shipping, Medidata Rave, and GlobalTrace.

To fulfill the training requirements, each participating site must have at least one staff member complete the training as noted below:

- At least one investigator from the enrolling site must complete the Protocol and Biospecimen Acquisition training modules.
  URL: https://coccg813.mindflash.com/PublicCoursePage.aspx?c=1483326417

AND

- At least one coordinator from the enrolling site must complete all five training modules: Protocol, Biospecimen Acquisition, Biospecimen Shipping, GlobalTrace, and Medidata Rave.
  URL: https://coccg813.mindflash.com/PublicCoursePage.aspx?c=1483397179

Questions regarding the Protocol or GlobalTrace training should be sent to the Study Chair Liaison at the DCC. Questions regarding the Biospecimen Acquisition and Biospecimen Shipping training should be sent to the Clinical Coordinator at the CL/B. Questions regarding Medidata Rave should be sent to the Data Manager at ECOG-ACRIN. See Appendix VII for contact information.

6.1 Protocol

The Protocol training module provides details necessary for conducting the study in compliance with the protocol. This includes site regulatory requirements, study background, objectives, study design, eligibility, visit schedule, data submission schedule, overview of specimen collection/submission, enrollment procedures, laboratory procedures, required pathology materials, and safety monitoring.

Questions regarding the Protocol training should be sent to the Study Chair Liaison at the DCC. See Appendix VII for contact information.

6.2 Biospecimen Acquisition and Biospecimen Shipping

The Biospecimen Acquisition and Biospecimen Shipping training modules detail specific procedures for specimen collection and packaging for shipment to the CL/B.

Questions regarding the Biospecimen Acquisition and Biospecimen Shipping training should be sent to the Clinical Coordinator at the CL/B. See Appendix VII for contact information.

6.3 Medidata Rave®

Required training in iMedidata for Data Entry Staff and Principal Investigators:

Once a user receives his/her study activation email and logs into Rave, s/he will be assigned eLearnings (i.e., online training modules). The eLearnings must be completed prior to starting data entry. General eLearnings only need to be completed once, prior to initial access to the first study.

CRAs performing data entry in Rave:

- Required eLearning:
  - Electronic Data Capture (EDC) Essentials for Clinical Research Coordinators
  - ECOG-ACRIN Supplemental Training
- Optional eLearning:
  - EDC Inspection Readiness for Clinical Sites
  - Data Privacy Considerations for Clinical Sites

Principal investigators and study chairs performing sign-off on CRFs in Rave:

- Required eLearning:
  - EDC Essentials for Investigators with Data Entry
  - ECOG-ACRIN Supplemental Training
- Optional eLearning:
  - EDC Inspection Readiness for Clinical Sites

Data Privacy Considerations for Clinical Sites

Questions regarding Medidata Rave should be sent to the Data Manager at ECOG-ACRIN. See Appendix VII for contact information.

6.4 Advantage eClinical/GlobalTrace℠

Advantage eClinical/GlobalTrace training is required for site personnel who prepare shipments of study specimens and pathology materials. The training details how to enter specimens, create electronic shipments, and generate the shipping manifest.

Questions regarding GlobalTrace should be sent to the contact at the DCC. See Appendix VII for contact information.

7.0 CLINICAL ASSESSMENTS

7.1 Study Visit/Data Submission Schedule

Table 7.1. The National MDS Study Visit/Data Submission Schedule

Procedure	Baseline	When medically indicated	Target Month (Specimen collection window is ±60 days)						Every 6 months
			6	12	18	24	30	36	
Medical History and epidemiologic exposures	X								
Tests performed in the prior 6 months: B12 level, serum folate, Mean Corpuscular Volume (MCV), Red cell distribution width (RDW), ferritin and Iron studies (Iron, TIBC, percent saturation)	X[7]								
Reticulocyte count	X								
VES-13	X								
Medical Examinations, Events, and Procedures[1]	X		X	X	X	X	X	X	X
Disease Staging (bone marrow aspirate required, and biopsy if performed)[2]	X	X[2]							
Peripheral Blood Sampling (CBC & Differential)[3]	X	X[3]	X	X	X	X	X	X	X
Germline DNA Collection[4]	X[4]			X[4]		X[4]			
QOL	X		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Bone Marrow Aspirate[6]	X	X							
Peripheral Blood Sample Shipment	X	X[2,3]	X	X	X	X	X	X	X
Slides for Central Pathology Review	X	X[2]							
Redacted Pathology and Cytogenetic Reports	X	X[2]							

[1]No other procedures are required by the protocol, but data will be requested from procedures performed for medical care.
[2]Subsequent disease staging should be performed as needed per standard of care.
[3]In addition to the scheduled collection every 6 months peripheral blood samples should be obtained when it is suspected that a participant has evolved to AML (often typified by progressive cytopenias and/or circulating blasts), and whenever a bone marrow aspiration is performed.
[4]Germline DNA samples will be extracted from the following materials: eyebrow hair follicles and buccal cells. Eyebrow follicles and buccal swab are required at baseline and may be optionally collected at 12 and 24 months.
[5]Post baseline, MDS cases and AML cases with < 30% blasts without core binding factor or APL complete the 4 questionnaires (QUALMS, FACT-G Version 4, PROMIS Short Form v1.0 – Fatigue 7a, and EQ-5D-5L), and ICUS cases and At Risk cases complete only the PROMIS Short Form v1.0 – Fatigue 7a, and EQ-5D-5L. After one year, the QOL instruments are completed annually.
[6]Harvest only the 1st or 2nd pull.
[7] If the participant is anemic, these tests should be performed in the prior 6 months.

7.2 Clinical Data Collection

Please refer to the NHLBI-MDS Data Management Handbook for further details on form structures and completion requirements.

Additional questions regarding the NHLBI-MDS Data Management Handbook or Medidata Rave should be sent to the Data Manager at ECOG-ACRIN. Clinical protocol questions should be sent to the Study Chair Liaison at the DCC. See appendix VII for contact information.

7.2.1 Enrollment Procedures

1. Informed consent will be obtained for data and sample collection.
2. Participant histories will be obtained and medical records will be reviewed to obtain past medical history, baseline laboratory tests, diagnostic information including reports and treatment history. **Note:** Entry of the participant's social security number at the time of enrollment is encouraged. This will allow researchers to link the study data with medical claims data in the future.
3. Participants will be asked to provide eyebrow hair follicles and a buccal swab at baseline. Hair follicles from the hairline may be submitted instead of or as a supplement to the eyebrow hair follicles.
4. Participants will be asked to contribute blood and bone marrow samples for storage.
5. Bone marrow, peripheral blood, and core biopsy slides will be centrally reviewed by study hematopathologists. If a sample is destroyed or un-usable, the study team may ask the clinic to re-contact some participants for additional samples. Failure to participate in the repeat test will not impact their care or treatment in any way. If the baseline samples are insufficient to classify the participant when submitted for the Central Pathology Review, the participant will not be followed long term.
6. Based on the Central Pathology Review, a baseline classification into the longitudinal cohort of cases (MDS, MDS/MPN overlap disorders, AML with < 30% blasts without core binding factor or APL, ICUS, or at-risk [dysplastic and selected genetic markers])) or the cross-sectional cohort (all others) will be made. Follow-up will occur based on these classifications and will not be altered by subsequent clinical events.
7. No post baseline biological samples or data will be captured for those classified into the cross-sectional cohort.
8. No post baseline biological samples or data will be collected from individuals who enroll and are classified as MDS, MDS/MPN overlap disorders, AML with < 30% blasts without core binding factor or APL, or ICUS after the relevant category-specific sample size limits have been reached.
9. Sites will be notified by an email message when the participant has been assigned to a study cohort. Site staff must log into Medidata Rave to complete the Cohort Assignment form.
10. Capture of biologic samples will be discontinued if the participant receives an HCT. Additional data may be collected from the Center for International Blood and Marrow

Transplant Research (CIBMTR) on participants receiving a transplant using the CIBMTR Recipient ID reported on the Transplant Form in Medidata Rave.

11. Biologic samples are submitted for cases in the longitudinal cohort at the time of AML diagnosis. Subsequent samples will not be collected for AML cases with > 30% marrow blasts, core binding factor, or acute promyelocytic leukemia.
12. Individuals may participate in other studies but will continue to submit data and specimens for this protocol.

7.2.2 Data Collected at Baseline

The following information from the participant's medical history and physical examination will be recorded at the time of enrollment with the baseline study visit:

1. Demographics
2. Site diagnosis
3. Blood counts and bone marrow assessment (Note that the blood counts should be recorded from the time the bone marrow assessment was performed)
4. Past medical history
5. Physical examination
6. Past year medications
7. QOL
8. Hospitalizations/Intensive care unit (ICU) admissions past 6 months
    a. Dates
    b. Reasons
9. Transfusions past 6 months
    a. Dates
    b. Number of units
10. Infection requiring antimicrobial therapy
11. Environmental exposures (including smoking, alcohol, and approximately 20 solvents)
12. Screening frailty assessment using the VES-13
13. Charlson Comorbidity Index
14. Novel Coronavirus Disease 2019 (COVID-19) Evaluation
15. Military History

This information will be reported on electronic Case Report Forms (CRFs) in Medidata Rave.

7.2.3 Diagnostic Procedures at Baseline

The following diagnostic procedures are required at baseline for all participants:

1. Peripheral blood complete blood count (CBC) with differential and reticulocyte count
2. Bone marrow aspiration (required)
3. Bone marrow biopsy (optional)
4. Conventional cytogenetics
5. If anemic, the following tests performed in the prior 6 months:

a. B12 level
b. Serum folate
c. Mean corpuscular volume (MCV)
d. Red cell distribution width (RDW)
e. Ferritin

f. Iron studies (Iron, Total Iron-Binding Capacity (TIBC) Test, percent saturation)

In addition, the following evaluations may be performed, but are not required for the study. Data should be provided if they are performed:

1. Fluorescence in situ hybridization (FISH)
2. Molecular analysis
3. Red blood cell (RBC) folate level
4. Comprehensive metabolic panel
5. Erythropoietin (EPO) level
6. Paroxysmal Nocturnal Hemoglobinuria (PNH) test
7. Lactate dehydrogenase (LDH)
8. Serum protein electrophoresis
9. Rheumatoid Factor
10. T cell receptor (TCR) rearrangements
11. Antinuclear antibody (ANA) test
12. Copper, serum
13. Direct antiglobulin test
14. Creatinine
15. Calculated glomerular filtration rate (GFR)
16. Thyroid-stimulating hormone (TSH) test

7.2.4 Data Collected at Follow-up

The following data will be recorded from the participant's medical and physical examination at follow-up visits every 6 months:

2. Disease evaluation including blood counts
3. Physical examination
4. MDS therapy
5. Transplant status
6. Hospitalizations/ICU admissions since last visit
   a. Dates
   b. Reasons
7. Transfusions since last visit
   a. Dates
   b. Number of units

8. Frequency of infectious complications
9. Adverse events
10. Concomitant therapy
11. QOL*
12. Malignancy
13. Survival status
14. COVID-19 Evaluation

This information will be reported on electronic Case Report Forms (CRFs) in Medidata Rave.

*QOL will be collected at baseline, 6 months, 12 months, and then yearly thereafter. Post baseline, MDS participants will complete QUALMS, FACT-G Version 4, PROMIS Short Form v1.0 – Fatigue 7a, and EQ-5D-5L. Post baseline, ICUS and At Risk participants will complete only the PROMIS Short Form v1.0 – Fatigue 7a and EQ-5D-5L.

7.2.5 Procedures at Follow-up

The following procedure is required at follow-up visits every 6 months:

1. Peripheral blood and complete blood count (CBC) with differential

Peripheral blood should also be obtained when it is suspected that a participant has evolved to AML (often typified by progressive cytopenias and/or circulating blasts), and whenever a bone marrow aspiration is performed

In addition, the following procedures may be performed as needed per standard of care during follow up. **Bone marrow samples and data should be submitted when the following procedures are performed:**

1. Bone marrow aspiration and biopsy
2. Conventional cytogenetics
3. Fluorescence in situ hybridization (FISH)
4. Molecular analysis

7.3 Quality of Life Administration

The study will perform assessments of QOL at baseline, 6 months, 12 months, and then yearly thereafter (Table 7.3.1) using the following instruments:

- Quality of Life in Myelodysplasia Scale (QUALMS)
- Functional Assessment of Cancer Therapy – General (FACT-G Version 4)
- Patient Reported Outcomes Measurement Information Systems (PROMIS) Short Form v1.0 – Fatigue 7a
- EQ-5D-5L

All participants will complete the 4 questionnaires at baseline. Post baseline, MDS cases and AML cases with < 30% blasts without core binding factor or APL will complete the same 4

questionnaires, while ICUS and At Risk cases will complete only the PROMIS Short Form v1.0 – Fatigue 7a and EQ-5D-5L..

Table 7.3.1. QOL Assessment Schedule – Longitudinal MDS, MDS/MPN, and AML Participants

QOL Survey	Baseline	Target Month (Collection window is ±60 days)		Every 12 months after one year
		6	12	
QUALMS	X	X	X	X
FACT-G Version 4	X	X	X	X
PROMIS Short Form v1.0 – Fatigue 7a	X	X	X	X
EQ-5D-5L	X	X	X	X

Table 7.3.2. QOL Assessment Schedule – Longitudinal ICUS and At Risk Participants

QOL Survey	Baseline	Target Month (Collection window is ±60 days)		Every 12 months after 1 year
		6	12	
QUALMS	X			
FACT-G Version 4	X			
PROMIS Short Form v1.0 – Fatigue 7a	X	X	X	X
EQ-5D-5L	X	X	X	X

Samples of the participant-completed questionnaires (QOL assessments and the VES-13) are included in Appendix IV. The paper copies of the QOL questionnaires for study participant completion must be obtained from the CTSU study page with the study materials.

Paper copies of the surveys will be completed by participants during their study visits. Participants should be instructed to respond to the questionnaires in terms of his/her experience during the time frame specified on each questionnaire. Participants must read the questionnaire instructions and complete all items. Site staff can assist the participant with completion of the questionnaires as long as they do not influence the participant's response. The study participants can expect to spend approximately 20 minutes completing the questionnaires at each visit.

As soon as the participant completes the questionnaires, the study nurse or research coordinator at the site must review to ensure all items were marked appropriately.

- If more than one answer was marked, the participant should be asked to choose the answer which best reflects how he/she is feeling.
- If a question was not answered, the participant should be asked if he/she would like to answer it. The participant should always have the option to refuse.
- If the participant refuses, it should be indicated on the questionnaire that he/she declined to answer the item.
- If the participant cannot complete a questionnaire or they refuse to complete the questionnaire, the reason must be noted according to the instructions in the NHLBI-MDS Forms Completion Guidelines.

After ensuring the questionnaire is complete, site staff must enter the data in Medidata Rave.

8.0 BIOSPECIMEN COLLECTION AND SHIPPING

8.1 Distribution of Specimen Collection Kits

Specimen collection kits will be sent to the clinical sites from the CL/B after all regulatory documents have been submitted and training related to the protocol and sample collection and shipment have been completed. An overview of the process is provided in Appendix VI Sample Collection Overview. For additional questions, contact the Clinical Coordinator at the CL/B. See Appendix VII for contact information.

8.1.1 Labeling System

The CL/B will prepare specimen collection kits that are unique to each tissue type. Each kit will contain the sample collection material required for the specific tissue type and will have a pre-assigned barcode on the outside of the collection kit to aid in tracking. A label with a barcode will also be included on collection tubes and containers.

The sample collection kit numbers can be entered manually in GlobalTrace, but it is recommended that sites utilize barcode scanners to scan the labels. Please contact the CL/B representative below if your site does not have a 1D barcode scanner available:

Mary Ellen Walker, RN, MSN
CL/B Clinical Coordinator at 813-745-5033
MDS_CLB@moffitt.org

8.2 Overview of Specimen Collection

Samples must be submitted as outlined below. Shipping details are included in Section 8.5.

Table 8.2. Biological Materials to be Collected and Shipped to the CL/B

Material	Baseline	Collect when medically indicated bone marrow aspiration is performed	Every 6 months during follow-up (±60 days from the target visit dates)	Optionally at 12 and 24 months	**Suspected progression to AML**	**Ship To:**
Bone marrow (5-10 mL heparin sodium tube)[1]	X	X				CL/B (Refer to Section 8.5)
Bone marrow (3 mL purple top tube with EDTA)[1]	X	X				
Germline tissue (12 eyebrow hairs with follicles [6 eyebrow hairs from each eyebrow[3]] and 2buccal swabs,)	X			X		
Peripheral blood (2 10 mL heparin sodium tubes)[2]	X	X	X		X	
Peripheral blood (3 mL red top tube)[2]	X	X	X		X	
Peripheral blood (8.7 mL PAXgene DNA extraction tube)[2]	X	X	X		X	
Peripheral blood (2.5 mL PAXgene RNA extraction tube)[2]	X	X	X		X	
Pathology Slides (See Section 8.4)	X	X[1]				

[1]Subsequent bone marrow samples should be collected as needed per standard of care.

[2]Peripheral blood samples should be obtained every 6 months during follow-up and when it is suspected that a participant has evolved to AML (often typified by progressive cytopenias and/or circulating blasts), and whenever a bone marrow aspiration is performed.

[3]Hair from the hairline may be submitted instead of or as a supplement to the eyebrow hair. The follicle must be obtained.

8.3 Procedures for Specimen Collection

Questions regarding specimen collection procedures in the sections below should be directed to the Clinical Coordinator at the CL/B. See Appendix VII for contact information.

8.3.1 Germline Control for Genetic Testing

Multiple somatic mutations have been identified in MDS. For accurate genetic description and somatic assignment, DNA that has been isolated from cells and is free from contamination with blood cells is required as a control. The following samples will be required at baseline and then optionally collected at 12 and 24 month visits.

8.3.1.1 Eyebrow Hair Follicle Collection

1. A nurse or study coordinator who is permitted to collect biospecimens should perform the eyebrow hair follicle collection. It has been documented that sample collection by a trained investigator leads to better consistency and higher DNA yield upon analysis. Note: Hair follicles from the hairline may be submitted instead of or as a supplement to the eyebrow hair follicles.
2. Explain the procedure to the participant, including the reason for eye brow hair collection.
3. Perform hand hygiene.
4. Position the participant near a window with natural light, if possible, or under a bright light with a good mirror and angled tweezers.
5. Brush brows up and out with their fingers.
6. Tweeze hairs in the direction they grow. Grab one hair at a time and hold skin taut when plucking. It is critical for the hair follicle to be attached to the hair shaft.
7. Use the sterile tweezers to place each eyebrow hair in the sterile tube provided.
8. Collect 6 hairs from each eyebrow.
9. Close the collection tube tightly.
10. Place the collection tube back into the biohazard bag that it was shipped in from the CL/B. Only use the specimen bag from the "Eyebrow Hair Follicle Kit" because the barcode on the bag is linked to the eyebrow hair collection/transport tube.
11. Ensure the sample is labeled correctly and the barcode on the biohazard bag is scanned into GlobalTrace.
12. Proceed to sample shipment or move to the next sample to be collected.

8.3.1.2 Buccal Swab Collection

PLEASE READ CAREFULLY AS INSTRUCTIONS HAVE CHANGED

Buccal Swab Schedule: Collect at baseline and optionally collected at 12 and 24 months

Materials in Buccal Swab Collection Kit:

- Two-5" cotton buccal swabs
- Biohazard Specimen Transport Bags with absorbent paper

- Sample Collection Instruction sheet
- Store sample collection kit at ambient temperature until ready to use

Procedure for Buccal Swab Collection (see training slides or MOP Section 8 entitled "Biospecimen Collection and Shipping" for additional detailed instructions):

1. Instruct the participant to not eat or drink 30-60 minutes prior to collection
2. Explain procedure to the participant and perform hand hygiene
3. An 11-digit Kit identification (ID) number starting with "BAT" and barcode are located on the outside of each kit to help in tracking
4. Scan the kit barcode into Global Trace (GT) (or manually enter the kit ID into GT) and it will populate the collection swabs within the electronic system
5. After the Kit ID is entered in GT, ensure the swabs in the bag match those populated in GT
6. Remove the swabs and barcode labels from the red biohazard bag
7. Rinse mouth for 20 seconds with water and expectorate the rinse
8. Remove one cotton swab from the sterile packaging
9. Swab the inner cheek for 30 seconds while rotating swab to cover all surfaces of the swab
   - Insert the swab into the mouth between the inside of the cheek and the upper gum line. Press firmly and twirl the brush against the inside of the inner cheek using an up and down motion from front to back and back to front. Cover as much cheek area as possible.
10. Allow swab to air dry by holding it in your hand for 1 minute; this minimizes the chances that the collected cells will become stuck within the transport tube.
11. Place the swab back into the transport container
12. Adhere one of the enclosed barcode labels to the transport container
13. Repeat steps 8-12 with second cotton swab on opposite cheek
14. Place both swabs back into the biohazard bag with absorbent material
15. Proceed to sample packaging for shipment
16. Ship samples on the day of collection **"FedEx First Overnight"** for receipt at the CL/B within 24 hours
17. If samples are collected on Friday, please send them for **"Saturday Delivery" and "FedEx First Overnight"**



8.3.2 Peripheral Blood Collection

The peripheral blood collection kit includes all pre-labeled tubes necessary for peripheral blood collection. 34.2 ml of blood is required at each sampling point. Please collect the blood in the following prioritized order:

Order of Draw	Tube
1) 3 ml in a red top tube (serum collection)	
2) 20 ml in a green top (sodium heparin) tube (10 ml in each tube)	
3) 8.7 ml in a PAXgene DNA Extraction tube	
4) 2.5 ml in a PAXgene RNA Extraction tube	

1. Please collect blood samples in the order noted above and allow each tube to fill to maximum volume. All efforts should be made to collect the maximum volume requested.
2. If lesser volumes are obtained, the sample should be shipped in accordance with instructions and the collected volume documented in GlobalTrace.
3. The PAXgene blood RNA tube should be the last tube drawn in the phlebotomy procedure to allow for time to quickly invert the sample as follows:
   - After blood collection, gently invert the PAXgene blood RNA tube and the PAXgene DNA tube 8-10 times.
4. Store the PAXgene blood RNA and PAXgene blood DNA tubes upright at room temperature until shipped. Samples are required at study entry, every 6 months, and whenever a bone marrow aspiration is performed. Peripheral blood samples will be collected according to each facility's Standard Operating Procedure.

5. After the samples are collected, ensure they are labeled correctly and the specimen collection kit barcode is scanned into GlobalTrace.
6. Proceed to sample shipment.

8.3.3 Bone Marrow Aspiration

Bone marrow assessments will **ONLY** be conducted as part of routine clinical care, always at entry to the study and subsequently when clinically necessary. Bone marrow aspirations will be performed per the facility's standard of care.

1. When a bone marrow aspirate is performed, 13 ml of bone marrow aspirate is requested. **Only 1st or 2nd pulls should be submitted.**
2. The bone marrow biospecimen collection kit includes two pre-labeled tubes necessary for bone marrow collection. Please collect bone marrow samples in the order noted below with the indicated volume. **Note: Care should be taken to ensure that the bone marrow sample does not become clotted at the time of acquisition.**

Order of Draw	Tube
1) 5-10 ml in a green top (sodium heparin) tube	
2) 3 ml in a purple top (EDTA) tube	

3. After the samples are obtained, invert each tube multiple times to prevent coagulation.
4. Ensure the tubes are labeled correctly and the specimen collection kit barcode is scanned into GlobalTrace.
5. Proceed to sample shipment.

8.4 Pathology Materials

Submission of pathology materials for diagnostic review is mandatory for the participant to be considered evaluable. Failure to submit pathology materials may render the case unevaluable. Only first or second pulls should be used to prepare the pathology materials.

NOTE: 1. The bone marrow aspirate is required within 30 days of enrollment
2. The pathology slides should be submitted to the CL/B no more than 7 days after the aspiration procedure.

8.4.1 Pathology Reports

Pathology information and a redacted copy of the surgical pathology report will be uploaded in Medidata Rave. In addition, all information available on karyotype, FISH, and molecular genetic studies that have been performed at the home institution will be uploaded.

Please note, all documents must be redacted at the site prior to uploading in Medidata Rave. Identifiable information such as participant name or initials, participant ID, birth date, medical record number, physician name, and site information, must be removed. The redaction tool should be used to remove this information from PDF documents without obscuring the pathology information.

Questions regarding pathology materials should be sent to the Clinical Coordinator at the CL/B. See Appendix VII for contact information.

8.4.2 Pathology Material Required at Baseline

- 3 Peripheral Blood smears unstained, 1 Wright-Giemsa (W/G) stain (optional)
- 3 Bone Marrow aspirate smears unstained, 1 W/G stain (optional), 1 Prussian blue stain (optional); unbound preferred
- 1 Bone Marrow biopsy hematoxylin and eosin (H&E) stained is required if biopsied
- 1 unstained bone marrow core biopsy is required if biopsy procedure was performed
- 1 touch preparation slide is required if dry tap occurs

Additional instructions for preparation of pathology materials:

- Please work with your local pathology group to ensure that extra peripheral blood and bone marrow slides are prepared for this study.
- The pathology group should label slides with specimen type, site code, subject ID, and tissue/stain type (*NOTE: these slides will NOT have an individual barcode to scan).*
- The container (slide box) for the slides will be pre-labeled with a unique barcode label to be scanned into GlobalTrace for shipment tracking.
- When a bone marrow core biopsy is performed, please ensure the following samples are submitted when they are released from pathology:
    - 1 unstained core biopsy
    - 1 H&E stained core biopsy
- Place the samples in the "Core Biopsy Kit" slide box and scan the unique barcode label on the slide box into GlobalTrace for shipment tracking
- *** *A touch prep imprint should not be considered a substitution for the core biopsy sample unless there was a dry tap. PLEASE NOTE: the difference between a touch*

prep and core biopsy slide is that touch preps are made from repetitive touching and lifting of the core onto the slide, while core biopsy slides are made from FFPE fixed core material prepared by histology

Please see below for further clarification.

Pathology Material Required for Central Review					
		Unstained	**Wright Giemsa***	**Prussian Blue (iron)***	**H&E***
Peripheral Blood	**required**	**3 slides**			
	optional		**1 slide**		
Bone Marrow Aspirate	**required**	**3 slides**			
	optional		**1 slide**	**1 slide**	
Bone Marrow Core Biopsy	**required if biopsied**	**1 slide**			**1 slide**

8.4.3 Pathology Material Required at Subsequent Bone Marrow Assessments

- 3 Peripheral Blood smears unstained, 1 W/G stain (optional)
- 3 Bone Marrow aspirate smears unstained, 1 W/G stain (optional), 1 Prussian blue stain (optional); unbound preferred
- 1 Bone Marrow biopsy H&E stained is required if biopsied
- 1 unstained bone marrow core biopsy is required if biopsy procedure was performed
- 1 touch preparation slide is required if dry tap occurs

Additional instructions for preparation of pathology materials:

- Please work with your local pathology group or clinical investigators to ensure that extra peripheral blood and bone marrow slides are prepared for this study.
- The pathology group should label slides with type of specimen, site code, subject ID, and tissue/stain type (*NOTE: these slides will NOT have an individual barcode to scan)*
  - When a bone marrow core biopsy is performed, please ensure the following samples are submitted when they are released from pathology:
    - 1 unstained core biopsy
    - 1 H&E stained core biopsy
- Place the samples in the “Core Biopsy Kit” slide box and scan the unique barcode label on the slide box into GlobalTrace for shipment tracking

NOTE: Subsequent pathology materials have the same requirements as at baseline; please refer to the above table for additional clarification.

8.5 Shipping of Specimens and Pathology Materials

Samples are to be shipped within 24 hours of collection to the CL/B. Samples collected on Friday must be sent for Saturday delivery.

Based on the timing and location of bone marrow procedures, multiple shipments at different time points may be necessary. In the event blood and bone marrow specimens must be collected from different procedures, it may be necessary to create additional shipments if the participant has to return for the bone marrow biopsy or if the bone marrow biopsy is done at another location. In that case, ship germline samples as instructed at the time of the initial visit. The second shipment would contain the bone marrow and peripheral blood specimens. The third shipment would contain the pathology slides and a fourth shipment would contain the bone marrow core biopsy slides.

Ship all biospecimens Monday through Thursday "FedEx First Overnight" for first overnight delivery. Samples collected on Friday should be sent via FedEx for "Saturday Delivery". Please send all samples to the following address:

MDS Central Laboratory and Biorepository
MIOMS
10902 N. McKinley Drive
Tampa, FL 33612
Ph: 813-384-6726
Attn: Jeff Painter

The FedEx account number is available in GlobalTrace by clicking the 'FedEx Account Number' link on the Data Entry tab.

NOTE: Each sample collection kit will contain a variety of sample collection containers such as pre-labeled blood collection tubes, pre-labeled germline sample collection materials, pre-labeled slide box for the pathology slides, and pre-labeled bone marrow collection tubes. If for any reason an individual specimen is not collected, enter that the tube was not used in GlobalTrace. This ensures that kits stay intact and inventory remains consistent for the expected specimen submissions and the actual specimen submissions. Please refer to GlobalTrace training documents for further information.

Each kit will include an expiration date on the kit label. If a kit expires prior to use at your site, please notify the CL/B and dispose of the kit at your site.

Do not send samples to Moffitt Cancer Center.

Questions regarding specimen shipment should be sent to the Biorepository Specialist at the CL/B. See Appendix VII for contact information.

8.5.1 Shipping Supplies

1. Blood Transport Sleeves
2. Absorbent material
3. Plastic Transport Tubes labeled with the UN3373 Label

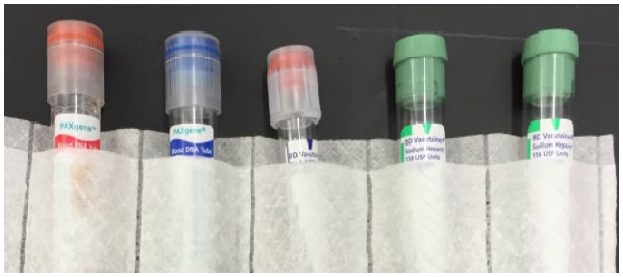
4. FedEx UN3373 Transport bags

8.5.2 Ambient Shipping Procedures for the Germline Samples – Eyebrow Hair and Buccal Swabs

1. Barcodes will be present on the outside of the sample collection kit and on the collection containers when supplies are sent from the CL/B.
2. After the samples are collected, scan the kit ID numbers into GlobalTrace and that will populate the tubes/containers within the electronic system for that sample type.
3. Place samples back into their labeled specimen collection bag.
4. Ensure all tubes in the specimen collection bag match those populated in GlobalTrace for that sample type.
5. Create a sample manifest and place a copy of the manifest inside the FedEx Overpack 3373 along with the samples.
6. Notify FedEx for sample pick-up or deliver package personally to a FedEx location. NOTE: **DO NOT place samples in a FedEx drop box.**

8.5.3 Shipping Procedures for Bone Marrow and Peripheral Blood

1. Place blood or bone marrow samples into the blood transport sleeve that is included in the sample collection kit. Roll up the sleeve and return it back into the biohazard bag for that sample type.





2. Ensure each sample type is placed into the biohazard bag for that specimen type! The barcode label located on the outside of each specimen collection kit is linked to those samples!
3. Scan the barcode on the specimen collection kit into GlobalTrace.
4. Seal the biohazard bag.
5. Place each specimen collection kit biohazard bag with their respective samples into a UN3373 plastic transport containers provided.



6. Create a sample manifest in GlobalTrace and place a copy inside the FedEx Overpack 3373.
7. Be sure all samples are placed into the FedEx Overpack3373.
8. Notify FedEx for sample pick-up or deliver package personally to a FedEx location. NOTE: **DO NOT place samples in a FedEx drop box.**

8.5.4 Shipping Procedures for the Histopathology Slides

1. Please work with your local pathology group to ensure that extra peripheral blood and bone marrow slides are prepared for this study.
2. The pathology group should label all slides with specimen type, subject ID, site ID, and tissue/stain type (NOTE: these slides will NOT have an individual barcode to scan).
3. Place the labeled slides into the slide box and place the slide box back into the "slide box" biohazard bag.
4. Scan the barcode from the "slide box" biospecimen bag into GlobalTrace.
5. Standard mailing containers (canisters, padded envelopes) are designed to transport specimens such as prepared slides.
6. The slides do not require special temperatures or handling.
7. To prevent slides from breaking, please use the proper transport container, (such as a padded envelope) or add sufficient packing material to make sure the slides will not break if dropped from a 4 foot height.
8. The slides can be sent using US mail or the designated FedEx account.
9. **NOTE: When a core biopsy is sent to the CL/B, please follow the above instructions and use the "Core Biopsy Kit" slide box provided in the biohazard bag.**
10. **Be sure to scan the individual barcode on the core biopsy slide box to enter the sample into GlobalTrace.**
11. **Proceed as above for slide shipments to the Central Laboratory and Biorepository.**

8.5.5 Shipping Procedures for the FedEx OverPak

1. FedEx OverPak shipping bags are pre-labeled with UN3373 and Class B labels according to IATA PI650.
2. After samples are scanned and packaged for shipment, complete the FedEx label and attach to the mailing pouch as indicated.
3. The FedEx UN3373 shipping bags will be included with the project supplies
4. All shipments are made at ambient temperature
5. Notify FedEx for sample pick up or deliver package personally to a FedEx location. Please refer to https://www.fedex.com/en-us/shipping/schedule-manage-pickups.html to schedule a FedEx pick-up or to locate the nearest FedEx drop off location.
6. DO NOT place samples in a FedEx drop box!

8.5.6 Procedure for Disposing Expired Sample Collection Kits

Unused, expired peripheral blood and bone marrow specimen collection kits distributed for the NHLBI-MDS protocol may be disposed of at the clinical site and **do not** need to be returned to the Central Laboratory and Biorepository.

Accepting Replacement Collection Kits in GT

1. To verify and accept kits recived from the CL/B, navigate to the **"Data Entry"** tab and click **"Kits Receiving".**
2. Select the shipment ID provided in the notification email sent when the CL/B ships the kits.
3. The **Speciment Kit Receiving Form** opens. Complete the form and click "**Save".**
4. Return the replacement sample collection kits to the study's supply inventory. Store all sample collection kits at ambient temperature.
5. Accept replacement kits in GlobalTrace as soon as they are received from the CL/B so that they are accessible in your site inventory. Note that it will not be possible to send electronic shipments if the kits have not first been received in GlobalTrace.
6. **Please use the kits that have the earliest expiration date first.**

8.5.7 Quality Control

This project is designed, in part, to develop a high quality specimen resource for future research efforts. This will be accomplished by creating a standardized clinical data-set linked to a prospectively collected, consistently processed, and well characterized biospecimen repository from the study participants. Therefore, attention to detail and quality control measures are essential to ensure the success of this project.

Site performance will be evaluated on:

- Sample collection and shipping times are documented
- Properly packaged shipments to keep specimens from being damaged during shipment
- Proper use of biohazard bags for the shipments
- Data availability for Central Pathology Review
- Volume of blood and bone marrow collected (required versus actual)
- Complete sample collection for each enrolled participant

Site quality metrics are based on a comparison of specimen QC results across all sites

- Presence of bone marrow spicules in the bone marrow aspirate tube
- Adequately stained bone marrow smears shipped for pathology review
    - Nucleic acid integrity and quantity
    - Cell viability for isolated cells from peripheral blood and bone marrow
- QC will be an ongoing process and the CL/B will work with each site, as needed, to identify and remedy problems.

Remedial Action Plan

- Outliers will be flagged

- Subsequent specimen sets will be monitored throughout processing for completeness and quality
- Any observable problematic trends will be investigated further
- Performance concerns will be addressed through follow-up conferences/meetings with appropriate site personnel to trouble shoot and offer guidance as necessary
- On-site evaluation/reassessment is possible in extreme situations

Participant Withdrawal

- Depending on clinical site and study-specific requirements for sample and data retention, the CL/B may:
    - At the request of the participant, specimens store at the CL/B and their derivatives will be properly disposed. Ensure appropriate system documentation
    - Maintain current specimens & derivatives with system annotation of participant status

Incomplete and Longitudinal Sample Sets

- Samples are collected according to the "Study Schema"
- In the event a specimen set is incomplete, the CL/B will coordinate with the submitting site and the DCC to track subsequent participant visits to determine if the sample can be re-collected.
- Similar coordination will apply to participants returning for another scheduled clinical collection event (bone marrow procedures)

8.6 Processing of Specimens

The CL/B will use Standard Operating Procedures (SOPs) to process specimens in accordance with College of American Pathologists (CAP) Biorepository Accreditation which is based largely on evidence-based collection of NCI Best Practices and International Society for Biological and Environmental Repositories (ISBER) best practices. CAP accreditation ensures that the day-to-day activities and services of the CL/B reflect these best practices for biospecimen processing and storage. QA and QC will be followed as defined in the CL/B SOPs.

All efforts should be made to collect the maximum volume requested. If lesser volumes are obtained, the actual amount collected should be entered into GlobalTrace. The sample should be shipped in accordance with instructions. Please document why the volume collected is less than the expected amount.

If a bone marrow aspirate or peripheral blood sample is received greater than 48 hours after acquisition, the sample will be processed, and the delay will be documented in LabVantage. The CL/B will follow up with sites if there are repeated delays in shipment.

Questions regarding shipments should be sent to the Biorepository Specialist at the CL/B. See Appendix VII for contact information.

8.7 Storage of Specimens

Linked and coded specimens will be stored at the CL/B based on the sample type. DNA and RNA will be stored at -80˚C and frozen cells will be stored in liquid nitrogen. Sample preparation for storage will follow defined SOPs that have been submitted to NHLBI and approved by the Protocol and Executive Committees. Samples may be released prior to the end of the study at the direction of the NHLBI. During the study, data associated with each specimen will be routinely transferred to the DCC and linked with the clinical data. At the conclusion of the study, specimens remaining at the CL/B will be transferred to the NHLBI Biorepository for long term storage and made available for future research. Specimens and the associated clinical data will be made available to qualified investigators through processes outlined on the BioLINCC website (https://biolincc.nhlbi.nih.gov/home/) and/or through communication with the Executive Committee.

8.8 Specimen Inventory at the CL/B

Specimens will be managed by Lab Vantage (LV) Solutions, which is a laboratory information management system (LIMS) from Somerset, NJ.

9.0 CENTRAL PATHOLOGY REVIEW PROCESS FOR STUDY ASSIGNMENT

Diagnostic material for the National MDS Study from the baseline bone marrow aspirate and peripheral blood smears must be submitted for Histopathology Review and study classification within 30 days of enrollment. Diagnostic materials will be centrally reviewed at baseline for all enrolled cases, at re-screening (if applicable), and post-baseline for cases enrolled in the longitudinal cohort when additional diagnostic bone marrow samples are collected. Pathology slides should be submitted within 7 days of the aspiration procedure. Submission of pathology materials for diagnostic review is mandatory for the participant to be considered evaluable. Failure to submit pathology materials may render the case unevaluable. Pathology materials will be shipped to the CL/B where they will be reviewed by Ling Zhang, MD, Associate Member, Department of Hematopathology and Laboratory Medicine, Moffitt Cancer Center and / or Lynn Moscinski, MD, Department Chair, Hematopathology and Laboratory Medicine, Moffitt Cancer Center.

In addition to submission of the pathology materials to the CL/B, the clinical site must assess each participant according to the WHO classification for MDS and enter this information on the Marrow Assessment form in Medidata Rave within 6 weeks of enrolling the participant. This classification is the site-assigned disease status which will be compared to the study assignment from the CL/B.

The following section describes the Central Pathology Review process for submitted pathology slide sets. The first 3 steps are applicable whenever a bone marrow aspiration procedure is performed. Steps (4 to 8) apply to bone marrow specimens at the time an individual enters the study and the initial study assignment is made.

1. Clinical Site

   After an individual enters the study, a bone marrow aspirate and an (optional) bone marrow biopsy are performed, and peripheral blood samples are obtained. The bone marrow aspirate and (optional) bone marrow biopsy must be done within 30 days of study enrollment.

   The associated pathology report(s) including all cytogenetic and genetic study results are submitted electronically through the data entry system. The pathology reports must be de-identified prior to uploading as described in Section 8.4 Pathology Materials. The cytogenetic/karyotype information and the final pathology assessment from the site should be uploaded as two separate documents in Medidata Rave.

   Pathology slides are submitted to the CL/B. Slides should be submitted no later than 7 days after the aspiration event.

2. CL/B Cytogenetics Scoring

   From the submitted cytogenetic reports, the responsible hematopathologist enters the relevant findings in the study database.

3. CL/B Pathology Review

A study pathologist (physician) at the CL/B with expertise in MDS will conduct a review of all participants enrolled in this study. Peripheral blood measurements, peripheral blood slides, bone marrow aspirate, and bone marrow slides from the site are required for this process.

4. Initial Study Assignment

   After review of the pathology slides from the baseline visit, relevant clinical information from the study database files, and cytogenetic results from the study data base, the study pathologist (physician) will make the preliminary study disease assignment. The individual will be classified as to their disease status (MDS, MDS/MPN overlap, ICUS, or Other) and, when applicable, the MDS World Health Organization (WHO) category will be assigned. These results will be recorded in the study database. At the time of entry of the classification, an assessment of dysplasia and cytogenetic abnormalities associated with the 'At Risk Longitudinal Cohort', as described in the protocol, will be recorded.

5. Comparison By Algorithm

   A comparison will be performed at the DCC by computer algorithm of the site-assigned disease status and the study assignment. If the 2 agree, the study assignment process is completed for all cases that are not classified as 'Other'. For the 'Other' cases, additional steps are described in number 8 below.

6. When Central and Local Study Assignment Disagree

   Pathology reports from the study database are made available to the study pathologist and the study site may be notified to allow for additional information to be submitted clarifying the diagnosis. Such notifications will not occur in real time and are not intended to assist in patient care.

   The study pathologist reviews available materials and can change their initial assessment, if appropriate. If the study assignment difference is attributable only to a small (<3%) difference in blast count percentage then the CL/B assignment will become the study assignment. The central pathologist may also conclude that an alternative site coding is consistent with the submitted observations i.e. a 'coding error' and not refer the case for 3rd party review. Otherwise, if a disagreement remains then proceed to the next step.

7. 3rd Party Pathologist Review

   The case will be referred to a study-designated external pathologist for the study assignment. The external pathologist is provided access to all submitted case materials. Until the external pathologist assignment is completed, the review pathologist assignment is used for study purposes. The external pathologist's assignment is used as the final study classification and his/her assessment completes the study assignment process for all cases that are not classified as 'Other'. For the 'Other' cases, additional steps are described in number 8 below. Such notifications will not occur in real time, and are not intended to assist in patient care.

8. Cases Classified as 'Other'
   When a final study classification is determined to be 'Other', an assessment will be made for inclusion in the 'At Risk Longitudinal Cohort' as defined in the protocol. The assessment will first look at the CL/B entered assessments of dysplasia and cytogenetics to determine if either meet the protocol defined criteria. If either do, the case will be assigned to the 'At Risk Longitudinal Cohort'. If neither criteria are met, the cohort classification will remain pending until the results of the central genetics panel are received. If either local or central assays identify mutations meeting the protocol defined criteria, the case will be assigned to the 'At Risk Longitudinal Cohort'. If none of the 3 protocol criteria are determined to be met, the case will be assigned to the 'Cross-sectional Cohort'.

9. DCC Notification to Clinical Site

   After the study assignment is completed, the DCC updates reports of the total number of longitudinal and cross-sectional participants. Based on the protocol plan, the study diagnosis and the current classification totals, the entering clinic site is informed in Medidata Rave whether longitudinal samples will be requested from the individual. This will occur as soon as practical and is planned to occur by the end of month 4. The study classification from the Central Pathology Review will not occur in real time and is not intended to assist in patient care.

   Similar processes will be used to review pathology materials from follow-up bone marrow biopsies/assessments.

10. Pathology Communication with Clinical Site (Special Cases)

    There may be special cases where information related to the central pathology review may need to be communicated between central pathology and the clinical site to support participant care. For this to occur, approval will be needed from the NHLBI COR and the Steering Committee chair (or vice chair if the chair is not available). Once those approvals have been received and formally documented, information will be shared directly by either the DCC or CL/B to the clinical site while maintaining participant confidentiality. These events will be reported to the OSMB on an annual basis. Such requests are anticipated to be rare (<1% of entrants) as this is an observational study and not intended to direct participant clinical care decisions.

10.0 SITE MONITORING

ECOG-ACRIN will monitor the site data quality using standard metrics which includes reports of overdue forms and open queries in Medidata Rave. Standard procedures will be followed for site monitoring and data management. The data management plan includes the study-specific procedures for data quality assurance.

Data Management questions should be sent to the Data Manager at ECOG-ACRIN. See Appendix VII for contact information.

10.1 OSMB Reports

The OSMB will provide safety oversight consistent with NHLBI policy. The DCC will prepare OSMB reports with the following data:

1. Cumulative accrual
2. Timing of site initiation as measured by initial case accession
3. Accrual by site
4. Data quality by site
5. Demographics
6. Study associated Serious Adverse Event (SAE) reports
7. Reasons for exclusion from the longitudinal cohort
8. Characterization of the longitudinal cohort
9. Comparison of site versus central pathology classification
10. Central Pathology Review process
11. Biospecimen/Pathology material submission
12. Longitudinal cohort biospecimen/pathology materials submission
13. Longitudinal cohort retention
14. Status of specimen/data requests

The CL/B will provide information related to the QA/QC of the samples received based on the metrics as noted in Section 8.5.6. Additional information related to follow up with the sites will be provided.

The OSMB will review the reports and make recommendations to the NHLBI regarding starting, continuing, or stopping the study.

11.0 ADVERSE EVENT REPORTING

11.1 Adverse Event Reporting and Management

As this study is observational, no treatment related adverse experiences are attributable to study therapy.

11.1.1 Definition of Adverse Event

The reportable adverse events for this study are severe adverse events (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3-5) related to the biologic sampling procedures for the study. These events should be recorded on electronic Case Report Forms (CRFs) in Medidata Rave.

Questions related to adverse event reporting should be sent to the Study Chair Liaison at the DCC. See Appendix VII for contact information.

12.0 HUMAN SUBJECT PROTECTION AND REGULATORY PROCEDURES

12.1 Institutional Review Board

This study is overseen by the CPC CIRB for those sites who participate in this initiative. For sites that do not use the CPC CIRB as the IRB of record, local IRB review and approval is required.

12.2 Health Insurance Portability and Accountability Act (HIPAA)

A template HIPAA Authorization form is generated by ECOG-ACRIN and posted on both the ECOG-ACRIN and CTSU websites for site use.

12.3 Office of Human Research Protections (OHRP) Institutional Assurances

All sites must hold a current Federalwide Assurance (FWA) prior to participating in NCI-funded clinical research studies.

12.4 Participation of Women and Ethnic Minorities

Women and members of minority groups and their subpopulations are eligible to participate in this trial.

13.0 RESPONSE TO DATA AND SPECIMEN REQUESTS

During the conduct of the National MDS study, data and specimen-based research activities will be performed. These activities will include protocol specific analyses and ancillary studies. It will be the responsibility of the Steering Committee to assist the NHLBI in the evaluation of these research efforts. It is understood that the available biospecimens are a limited resource that once used will not be available for future analyses so that careful consideration and prioritization of requests for their use is required. At the conclusion of the study, data and specimens will be maintained by the NHLBI BioLINCC specimen and database repository which will have responsibility for responding to requests after study completion.

Details describing data and specimen requests will be developed and included on the study website and as an appendix to the MOP at a later date.

14.0 PUBLICATION AND PRESENTATION POLICY

14.1 Policy Statement

The resources established by the National MDS Study are intended to facilitate studies of MDS natural history and to rapidly disseminate information on MDS to the wider community. Definitive contributions are made through publications in peer-reviewed literature. Abstracts, public presentations, electronic postings and data sharing also contribute to public knowledge, and are encouraged by the Study. Prior to public dissemination of National MDS Natural History study results, approval of the Publications Committee, the Steering Committee, and the NHLBI Contracting Officers is required. This includes methodological or position papers related to protocol development or operations.

Planned oral presentations, which are limited to the design or rationale of the studies, or to data from prior published results, are subject to the review policy described herein. Individuals making such presentations must confirm with the Publications Committee that the material will not be recorded, published or represented without Committee approval.

The National MDS Study will comply with NIH public access policies including submission of study results and final manuscripts (e.g., clinicaltrials.gov, PubMed central, etc.). The National MDS Study will comply with all journal requirements (e.g., modified copyright transfer agreements, disclaimers, etc.) as they relate to NIH policy.

Please see the Data Use agreement in section 3.11.

14.2 The Role of the Publications Committee

The Publications Committee is responsible for developing publication and presentation policies. All policies must be approved by the Steering Committee before implementation. The Publications Committee encourages publication and presentations of information from the National MDS Study. In executing its work, the individual members and committee consider its objectives:

- To stimulate scientific presentations and papers from associated investigators;
- To ensure and expedite orderly and timely reports to the scientific community of pertinent results and information from the study;
- To ensure that abstracts, presentations, and publications are accurate and objective, do not compromise the scientific integrity of and are relevant to the objectives of the National MDS Natural History Study;
- To ensure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognized in study-wide reports;
- To establish procedures that allow the Steering Committee and NHLBI to exercise review responsibility in a timely fashion for publications and presentations;
- To encourage manuscripts based on the information collected at study sites;

- To prevent overlap of published material and duplication of analyses includes as objectives

14.2.1 Membership

Members are identified from a slate of candidates selected by the Steering Committee and the NHLBI. Members may include investigators at clinical sites participating in the study, Steering Committee members or others identified by the NHLBI. The Executive Committee approves these selected individuals and appoints the Publications Committee Chair from among the members. The Publications Committee roster is maintained on the study website.

14.2.2 Amendments to Publication/Presentation Committee Guidelines

Changes to policies will be subject to review, amendment and approval by the Steering Committee.

14.3 Publication Committee Processes

14.3.1 Letter of Research Intent (LRI)

Investigators from within or without the Steering Committee may request to develop an idea or to research a topic. A Letter of Research Intent (LRI) submission form is available on secured area of the website and all researchers may request access to it. The Letter of Research Intent is reviewed and prioritized by the Steering Committee, with NHLBI approval of those studies going forward. The letter is directed to the Chair of the Steering Committee and submitted via the study website. Reviews will commonly occur at the next Steering Committee meeting. A listing of approved studies is posted on the public section of the website with the approved statements of interest posted on the secure section of the study website. The format is short (2page limit) and should identify specimen requirements and resources either needed or brought to the project. LRI's should not be submitted unless the research effort can be initiated within 12 months of the submission.

14.3.2 Provisional Authorship

Upon LRI approval, a provisional authorship list will be developed. Steering Committee members and top accruing centers as determined by the Publications Committee will be advised of the research effort and offered opportunity to join the writing committee. Centers will be encouraged to participate as authors for the effort.

14.3.3 Manuscript and Presentation Reviewer(s) Identification

At least one Publication Committee member will be identified as the individual responsible for monitoring progress and reviewing products of the LRI effort. It is anticipated that some Publication Committee members may be authors on a project and this or other conflicts of interest would preclude their filling the reviewer role. If necessary because of conflicts or requirements for special expertise, the Publications Committee Chair can identify ad hoc reviewer(s). If more than one reviewer is identified, majority decisions will prevail. The independent review will assure the effort responsibly addresses the study objectives and is consistent with study-wide policies.

14.3.4 Adjudication

All disagreements or conflicts not resolvable at the independent reviewer stage can be referred to the Publications Committee as a whole, where non-conflicted members will provide a majority ruling. NHLBI guidance will be provided as required during the adjudication process.

14.3.5 Submissions

The paper or abstract must be attached to the original LRI via the study website and the DCC will review authorship from the provisional list and distribute to relevant parties including the NHLBI program officers.

14.3.6 Timelines

The Publications Committee is committed to rapid review of papers, abstracts and presentations. Ideally the authors can keep the reviewer(s) advised of upcoming submission plans or deadlines.

- In all cases a paper must be provided at least two full work weeks prior to intended submission and after the authors have completed the paper.
- Abstracts and presentations must be submitted at least one full work week prior to planned submission. If during manuscript preparation, the writing lead is unable to complete the initial draft or other responsibilities in a timely fashion, the Publications Committee may reassign responsibilities to another author

14.4 Authorship Guidelines

Authorship guidelines are based on fairness, inclusion and stimulation of participation and compliance. Author rewards focus on intellectual input and effort extended during the lifecycle of the study. The Publications Committee is responsible for the development and modification of guidelines for determining authorship. Any written authorship guidelines are ratified by the Steering Committee prior to implementation.

Authorship on publications is a privilege commensurate with both personal and center contribution to the research being presented. The primary requirement for authorship of a publication is a substantive contribution to the research effort and is a reward for many aspects of contribution which may include: (1) membership and active participation in the protocol team; (2) active accrual to the protocol and assay performance (3) timely and accurate reporting of data; and, (4) active participation in Steering Committee activities. These activities may include participation in the following areas: hypothesis generation, concept development, protocol development, study implementation, subject enrollment, data collection, data analysis, and manuscript preparation and finalization. In most instances, contributions in several areas must occur, and in every instance, authors are expected to contribute to manuscript preparation and finalization.

The fundamental premise of authorship designation is the contribution to overall effort. The International Committee of Medical Journal Editors provides the following requirements for authorship:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND

- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

When possible, first and senior authorship positions on the manuscripts should be broadly shared. First and senior authorship on papers does not imply the same privilege on any subsequent manuscripts resulting from related sub-studies. An author may be removed from the final manuscript, for example, for failing to make substantive contributions to the paper/presentation.

14.5 Study Recognition and Acknowledgements

14.5.1 Study Attribution

All papers and abstracts must identify in either the title or authorship line the association with the study by naming The National MDS Natural History Study.

14.5.2 Acknowledgments

- General - Other investigators not part of the authorship list but who have made significant contribution to the conduct of the study, as well as staff from a Clinical Center, DCC, CL/B or NIH, are noted.
- Government Sponsors - Each manuscript and presentation must acknowledge all NIH funding sources for the study, including in every instance, NHLBI contracts HHSN268201400003I to the DCC and HHSN268201400002I to the CL/B, and NCI co-sponsorship to the NCORP and the participating Clinical Centers.
    - Suggested wording is as follows:

      The National MDS Natural History study has been supported by US Federal Government Contracts HHSN268201400003I and HHSN268201400002I from the National Heart Lung and Blood Institute and additional funding by the National Cancer Institute to clinical centers.

14.6 Study Website

The DCC will support the Publications Committee by maintaining a record of planned, ongoing and completed research projects, including a bibliography of published materials, on the study website.

15.0 APPENDIX I NHLBI-MDS SITE REGISTRATION PROCESS

1. Sites access NHLBI-MDS study information on the Cancer Trials Support Unit (CTSU) website.
2. The NCI's National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) adult sites can participate in the study. Site investigators and staff must be registered with Cancer Therapy Evaluation Program (CTEP) to access the study documents on the CTSU members' website. The CTEP Identity Access and Management (CTEP-IAM) application will be used for initial and annual registration with CTEP and to obtain a user account (See section 4.3 Site Registration and Activation in the MOP for details).
3. Site staff view the NHLBI-MDS Site registration requirements on the CTSU members' website.
    a. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
    b. Click on the Protocols tab in the upper left of your screen
    c. Click on the Lead Group = ECOG-ACRIN to expand, then select trial protocol NHLBI-MDS
    d. Click on the Site Registration Documents link
4. Sites should complete the following requirements for NHLBI-MDS site registration first and submit them to the CTSU Regulatory Office via mail, fax, or email*:
    a. Protocol, Biospecimen Acquisition, Biospecimen Shipping, GlobalTrace, and Medidata Rave training. Site personnel must complete the 5 training modules as noted below:
        i. At least one investigator from the enrolling site must complete the Protocol and Biospecimen Acquisition training modules.
        URL: https://coccg813.mindflash.com/PublicCoursePage.aspx?c=1483326417
        ii. In addition, at least one coordinator from the enrolling site must complete all five training modules: Protocol, Biospecimen Acquisition, Biospecimen Shipping, GlobalTrace, and Medidata Rave.
        URL: https://coccg813.mindflash.com/PublicCoursePage.aspx?c=1483397179
    b. Complete and submit the "The National MDS Study: Site Information Checklist" (Appendix III) to the CTSU Regulatory Office.
        i. On the Site Information Checklist, the site must identify at least one International Air Transport Association (IATA) certified staff member and also submit their IATA certificate with Site Information Checklist to the CTSU Regulatory Office.
        ii. The CL/B reviewer may contact the site directly (with a copy to the CTSU and the DCC) to resolve questions or comments.
        iii. Final approval for the enrolling site will be submitted directly from the CL/B to the CTSU Regulatory Office and is required prior to first participant enrollment.

5. Sites should then submit the required documentation to the CTSU Regulatory Office via the Regulatory Submission Portal. Sites utilizing local IRBs are responsible for submitting their IRB approval documentation to CTSU.

   Additional Requirements for NHLBI-MDS Site Registration:

   a. CTSU IRB Certification (for sites not participating via the NCI CIRB) **or** Signed HHS OMB No. 0990-0263 (replaces Form 310) **or** IRB Approval Letter
   b. CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
   c. Copy of the IRB approved Informed Consent Document

   Note: Regulatory documentation must be received and approved prior to shipment of sample collection kits from the CL/B to the sites.

6. Sites check their registration status by logging in to the members' section of the CTSU website and querying the Regulatory Support System (RSS). Sites will not receive formal notification of regulatory approval from CTSU.
7. The Data Coordinating Center (DCC) and CL/B receive notification when site regulatory requirements are met.
8. The CL/B will send the specimen collection kits and barcode scanner (if needed) to the site once all site regulatory requirements are met.
9. Site confirms receipt of the specimen collection kits.
10. Site enrolls study participants through Oncology Patient Enrollment Network (OPEN). OPEN initializes the participant in the Medidata Rave database. **Note**: There is usually a 5-10 minute lag between enrollment in OPEN and the participant appearing in Medidata Rave.
11. The DCC receives notification of enrollment and initializes the participant in GlobalTrace.

*CTSU Regulatory Office contact information:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878

16.0 APPENDIX II SITE TRAINING MATERIALS

Sites are provided with the following slide sets for each training module:

1. Protocol Training Slides……...**Page 67**
2. Medidata Rave Training Slides….....**Page 75**
3. GlobalTrace Training Slides…….**Page 81**
4. Biospecimen Acquisition Slides……...**Page 89**
5. Biospecimen Shipping Training Slides…….**Page 97**

PROTOCOL TRAINING SLIDES

The National Myelodysplastic Syndromes Natural History Study
Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

The National MDS Study Protocol Training

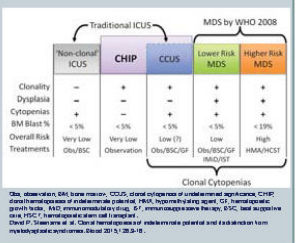
Table of Contents

- Study Background and Objectives – Slides 3-6
- Who is eligible? – Slides 7-14
- Protocol Overview – Slide 15
- Accrual – Slide 17
- Study Schema – Slide 18
- Data Submission and QOL – Slides 19-25
- Specimen Submission – Slides 26-37
  - Pathology Materials – Slides 28, 32, and 35
- Safety Monitoring – Slide 38
- Site Capitation and Credit – Slides 39-40
- Links and Contact Information – Slide 41

Study Background

The National Myelodysplastic Syndromes Natural History Study (The National MDS Study):

- Observational, prospective cohort study
- Long term follow-up of participants with MDS, idiopathic cytopenia of undetermined significance (ICUS), AML with <30% blasts without core binding factor or acute promyelocytic leukemia (APL)
- Establish a publicly available resource
- Facilitate the understanding of the natural history of MDS



What are Myelodysplastic Syndromes (MDS)?

- A group of clonal hematopoietic disorders
- Failure of the bone marrow to generate normal blood cells
- Results in one or more peripheral blood cytopenias
- *De novo* or therapy-related (from prior treatment of cancer)
- Patients experience fatigue, shortness of breath, easy bruising or bleeding
- Up to 30% of MDS transform to acute myeloid leukemia (AML)

- Additional information:
  - http://www.cancer.gov/types/myeloproliferative/hp/myelodysplastic-treatment-pdq#section/all

Why a natural history study?

To help future patients, adequate understanding of MDS natural history is required to:

- Improve MDS diagnosis, classification and prognosis
- Inform medical decision making
- Facilitate biomarker discovery
- Define the optimal use of existing therapies
- Identify new therapeutic targets
- Inform efforts to understand disease etiology and prevention



What are the study objectives?

- Create a multi-institutional, longitudinal biorepository
- Consistently process specimens from participants
- Collect clinical data linked to the specimens
- Support studies that will have high-impact for MDS patients including:
  - Basic science
  - Clinical and epidemiological research

Who is eligible?

a. Suspected MDS (e.g., persistent unexplained cytopenia, circulating peripheral blasts, etc.) or MDS/MPN overlap disorders and undergoing diagnostic work-up with planned bone marrow assessments

OR

b. Diagnosed with de novo or therapy-related MDS within 6-months of enrollment per the World Health Organization (WHO) criteria and undergoing clinical evaluation and planned bone marrow assessments to confirm MDS or to evaluate disease status

Who is eligible?

c. Bone marrow aspirate expected to be performed within 1 week of registration, and in all cases must be performed no later than 4 weeks after enrollment

d. Age 18 or older

Who is eligible?

e. No prior treatment for MDS at entry and through the time of the entry bone marrow aspirate

f. No treatment with hematopoietic growth factors in prior 6 months

Who is eligible?

g. If anemic without prior MDS diagnosis, the following tests should be performed within the prior 6 months. Values that are significantly outside of normal range do not exclude participation but should prompt investigation of alternative etiologies for anemia.
   - B12 level
   - Serum folate
   - Mean corpuscular volume (MCV)
   - Red cell distribution width (RDW)
   - Ferritin
   - Iron studies (Iron, Total Iron-Binding Capacity (TIBC) Test, Percent Saturation)

h. No diagnosis of a solid tumor or hematologic malignancy within two years prior to enrollment except for in situ cancer of the skin (basal or squamous cell), cervix, bladder, breast, or prostate

Who is eligible?

i. No treatment with radiation therapy in the two years prior to registration

j. No non-hormonal treatment for malignancy within the two years prior to registration

Who is eligible?

k. No established hereditary bone marrow failure syndrome

l. No known primary diagnosis of aplastic anemia, classical paroxysmal nocturnal hemoglobinuria, amegakaryocytic thrombocytopenic purpura, or large granular lymphocyte leukemia

m. Not enrolled in the Connect® MDS/AML Disease Registry

Should my patient go on this study?

In participants with suspected MDS and prior to registration, alternative causes for the cytopenias should be considered!

- Internal bleeding
- Autoimmune cytopenias
- Thyroid disorders
- Other causes of anemia

Does my patient have MDS?

In addition to the tests required for eligibility, the following tests could be performed to assist in the diagnostic work-up. **These evaluations are not required by the protocol.**

- Copper, serum level
- Direct Antiglobulin Test
- Antinuclear Antibody (ANA) Test
- Creatinine
- Calculated Glomerular Filtration Rate (GFR)
- Thyroid-Stimulating Hormone (TSH) tests

Protocol Overview

You suspect your patient has MDS...

- Enroll patient
- Collect clinical data (details in Table 1, slide 25)
- Collect peripheral blood specimens and bone marrow specimens (details in Table 2, slide 37)
- Send pathology slides for central review by the study hematopathologist (detailed in slides 32 and 35) and upload required reports
- Your site will be notified of the study assignment for each subject
  - Longitudinal cohort (follow-up needed every 6 ms): MDS, ICUS, or AML with <30% blasts without core binding factor or APL
  - Cross sectional cohort (no follow-up is required)

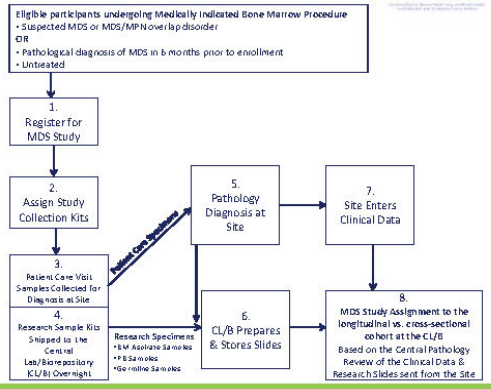
Study Participants

- Baseline pathology materials and data will be reviewed at the Central Lab
- Your site will be notified if the participant is assigned to the longitudinal cohort and should be followed long term

Target Accrual

- Longitudinal Cohort
  - **2000** participants with MDS, MDS/MPN overlap disorders, or AML
  - **500** participants with Idiopathic Cytopenias of Undetermined Potential (ICUS)
- Cross-Sectional Cohort
  - Up to 1000 additional participants
  - Participants in this cohort are eligible to be re-screened for participation if progression of signs or symptoms provides evidence to support a probable diagnosis of MDS, MDS/MPN overlap disorders, or ICUS

Study Schema



Enrollment and Data Submission

- Participants will be enrolled using the **Oncology Patient Enrollment Network (OPEN)**.
- Electronic data capture will be conducted in **Medidata Rave**.
- Specimen shipments will be tracked in **GlobalTrace**.

Data Collected at Baseline

1. Demographics
2. Site diagnosis
3. Blood counts and bone marrow assessment
4. Medical history and physical exam
5. Past year medications
6. QOL and frailty assessment
7. Hospitalizations/ICU admissions past 6 months
8. Charlson Comorbidity Index
9. Infections requiring antimicrobial therapy past 6 months
10. Environmental exposures (smoking, alcohol and ~20 solvents)

Optional Data at Baseline

If performed in the prior 6 months, submit the following:

1. Red blood cell (RBC) folate level
2. Comprehensive metabolic panel
3. Erythropoietin (EPO) level
4. Fluorescence in situ hybridization (FISH)
5. Molecular analysis
6. Paroxysmal Nocturnal Hemoglobinuria (PNH) flow cytometry (FLAER) on granulocytes
7. Lactate dehydrogenase (LDH)
8. Serum protein electrophoresis
9. Rheumatoid Factor
10. T cell receptor (TCR) rearrangements
11. Antinuclear antibody (ANA) test
12. Copper, serum
13. Direct antiglobulin test
14. Creatinine
15. Calculated glomerular filtration rate (GFR)
16. Thyroid-stimulating hormone (TSH) test

QOL (Quality of Life) Assessments at Baseline

- MDS-specific QUALMS
- FACT-G (Version 4)
- PROMIS Short Form v1.0 – Fatigue 7a
- EQ-5D-5L

Data Collected at Follow-up, Every 6 months

1. Disease evaluation
2. Physical examination
3. MDS therapy
4. Transplant status
5. Hospitalizations/ICU admissions since last visit
6. Transfusions since last visit
7. Frequency of infectious complications
8. Adverse events
9. Concomitant therapy
10. QOL
11. Malignancy
12. Survival status

Quality of Life (QOL) Assessments at Follow-up

The assessments listed below will be administered at 6 months, 1 year, and yearly thereafter.

- **MDS participants and eligible AML participants:**
  - MDS-specific QUALMS
  - FACT-G (Version 4)
  - PROMIS Short Form v1.0 – Fatigue 7a
  - EQ-5D-5L
- **ICUS participants:**
  - PROMIS Short Form v1.0 – Fatigue 7a
  - EQ-5D-5L

Data Submission Schedule

Data Collected	Baseline	When medically indicated	Every 6 months
Medical history and environmental exposures Baseline lab test results (within 6 months) Reticulocyte count VES-13	X		
Medical examinations	X		X
Disease staging (Whenever bone marrow aspirate, bone marrow biopsies, and blood smears are performed) Redacted pathology report and cytogenetic reports	X	X	
Peripheral blood lab results (CBC and differential)[1]	X	X	X
QOL (required yearly after 12 months)[2]	X		X

[1] Peripheral blood samples should be obtained when it is suspected that a patient has evolved to AML (often typified by progressive cytopenias and/or circulating blasts), and whenever a bone marrow aspiration is performed.
[2] Post baseline, MDS cases and eligible AML cases complete the 4 questionnaries. Cases entered with ICLIS complete only the PROMIS Short Form v1.0 – Fatigue 7a and EQ-5D-5L. After one year, the QOL instruments are completed annually.

Specimen Submission

- Study supplied kits will be used to submit all biological samples (hair follicles, buccal swab, bone marrow, peripheral blood, and pathology materials).
- Specimen kits should be shipped on the date of collection for receipt at the Central Lab/Biorepository within 24 hours. Samples collected on Friday must be sent for Saturday delivery.

Central Pathology Review

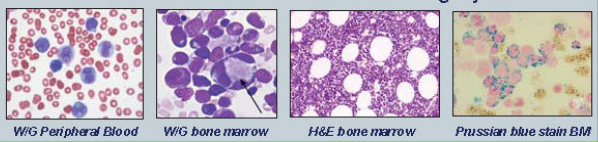
1. For uniform patient classification across multiple sites, Central Pathology review will be conducted at the CL/B under guidance of highly trained clinical hematopathologists.
2. Diagnostic material from the baseline visit must be submitted for review and classification.
3. Submission of pathologic materials for central review is mandatory and must be submitted within 7 days of the aspiration procedure.
4. Failure to submit pathologic materials may render the case unevaluable.

Slides for Central Review

Summary of slides required for Central Review

Pathology Material Required for Central Review					
		Unstained	Wright Giemsa*	Prussian Blue (Iron)*	H&E*
Peripheral Blood	required	3 slides			
	optional		1 slide		
Bone Marrow Aspirate	required	3 slides			
	optional		1 slide	1 slide	
Bone Marrow Core Biopsy	required if biopsied	1 slide			1 slide

*Stained slides are highly desirable



W/G Peripheral Blood | W/G bone marrow | H&E bone marrow | Prussian blue stain BM

Required Specimens at Baseline, Overview

- Samples used for Germline Controls in Genetic Testing
  - Hair follicles and buccal cells
- Peripheral Blood
- Bone Marrow Aspirates
- Pathology slides prepared from the peripheral blood and the bone marrow
  - Necessary for central hematopathology assessment

The following slides detail these requirements.

Required Specimens at Baseline

- Germline Controls for Genetic Testing
  - Hair Follicles: 12 eyebrow hairs with the follicles (6 hairs from each eyebrow)* (required)
  - Buccal Swab (required)

*Hair follicles from the hairline may be submitted instead of or as a supplement to the eyebrow hair follicles.

Required Specimens at Baseline

- Peripheral Blood (34.2 ml total)
  - 20 ml (10 ml in 2 green top sodium heparin tubes)
  - 8.7 ml (PAXgene DNA extraction tube)
  - 2.5 ml (PAXgene RNA extraction tube)
  - 3 ml (red top tube)
- Bone Marrow (~13 ml)
  - 5-10 ml aspirate (green top sodium heparin tube)
  - 3 ml aspirate (purple top EDTA tube)
  - **Only the 1st or 2nd pulls should be sent.**

Required Pathology Materials at Baseline

- 3 Peripheral Blood smears unstained (required)
  - 1 Wright-Giemsa (W/G) stain (optional)
- 3 Bone Marrow aspirate smears unstained (required); unbound preferred
  - 1 W/G stain (optional)
  - 1 Prussian blue stain (optional)
- 1 Bone Marrow biopsy hematoxylin and eosin (H&E) stained is required if biopsied
- 1 unstained core section is required if biopsied
- 1 touch preparation slide is required if dry tap occurs
- **The required slides for central hematopathology assessment must be sent within 7 days of procedure.**

Required Specimens at Follow-up

- Peripheral Blood (34.2 ml total)
  - 20 ml (10 ml in 2 green top sodium heparin tubes)
  - 8.7 ml (PAXgene DNA extraction tube)
  - 3 ml (red top tube)
  - 2.5 ml (PAXgene RNA extraction tube)



Additional Specimens at Follow-up

Bone marrow samples, and cytogenetics, FISH, and molecular data must be submitted when these procedures are performed as part of clinical care.

- Bone Marrow (~13 ml)
  - 5-10 ml aspirate (green top sodium heparin tube)
  - 3 ml aspirate (purple top EDTA tube)
- **Only the 1st or 2nd pulls should be sent.**

Pathology Materials at Follow-up

Required when Bone Marrow Assessments are performed during follow-up:

- 3 Peripheral Blood smears unstained (required)
  - 1 W/G stain (optional)
- 3 Bone Marrow aspirate smears unstained (required); unbound preferred
  - 1 W/G stain (optional)
  - 1 Prussian blue stain (optional)
- 1 Bone Marrow biopsy H&E stained is required if biopsied
- 1 unstained core section is required if biopsied
- 1 touch preparation slide is required if dry tap occurs

Optional Specimens at Follow-up

- Germline Controls for Genetic Testing (Optionally collected at 12-month and 24-month visits)
  - Hair Follicles: 12 eyebrow hairs with the follicles (6 hairs from each eyebrow)*
  - Buccal Swab

*Hair follicles from the hairline may be submitted instead of or as a supplement to the eyebrow hair follicles.

Sample Submission Schedule

Material	Baseline	Collected when disease assessment performed	Every 6 months during follow-up	At 12 and 24 months (optional)	Progression to AML
Bone marrow: • 5-10 ml in a sodium heparin tube • 3 ml in a purple top tube with EDTA	X	X			
Germline tissue: • 12 hair follicles (6 from each eyebrow; hair follicles from the hairline may be submitted) • Buccal swab	X			X	
Peripheral blood: • 2X 10 ml in sodium heparin tubes • 3 ml in red top tube • 8.7 ml in PAXgene DNA extraction tube • 2.5 ml in PAXgene RNA extraction tube	X	X	X		X
Pathology Slides: • 3 Peripheral Blood smears unstained (required) o 1 W/G stain (optional) • 3 Bone Marrow aspirate smears unstained (required) o 1 W/G stain and 1 Prussian blue stain (optional) • 1 Bone Marrow biopsy H&E stained, required if biopsied • 1 unstained core section, required if biopsied • 1 touch preparation slide, required if dry tap occurs	X	X			

Safety Monitoring

- As this study is observational, no treatment-related adverse experiences are attributable to the study.
- Report only severe (CTCAE grade 3-5) adverse events **related to study sampling procedures** via Medidata Rave.

Site Capitation

- **0.5 Credit (NCORP), $1250 (other NCTN sites)** for collection of baseline data and specimens from each participant who enters the study (Base Intervention)
- **An additional 0.5 Credit (NCORP), $1250 (other NCTN sites)** for each participant who enters the Longitudinal Cohort (determined by the Central Pathology Review)

NCTN Group Enrollment Credit Towards Membership Requirements

Separate from the capitation that is provided for each enrollment, the NCTN groups listed below are providing ***enrollment credit that can be counted towards each site's membership accrual requirements.***

NCTN Group	Enrollment Credit Applied to Membership
Alliance	1.0 credit for initial protocol enrollment for Base Intervention
ECOG-ACRIN	0.5 credit for initial protocol enrollment for Base Intervention 0.5 credit for any patient assigned to Longitudinal Cohort
NRG	1.0 credit for initial protocol enrollment for Base Intervention
SWOG	0.5 credit for initial protocol enrollment for Base Intervention 0.5 credit for any patient assigned to Longitudinal Cohort

Links and Contact Information

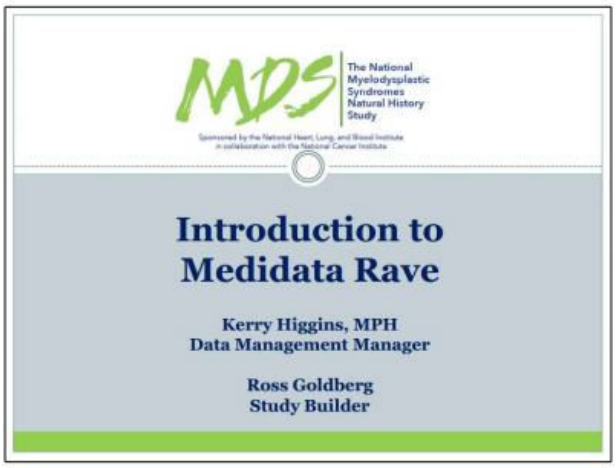
Study Website: https://thenationalmdsstudy.net/

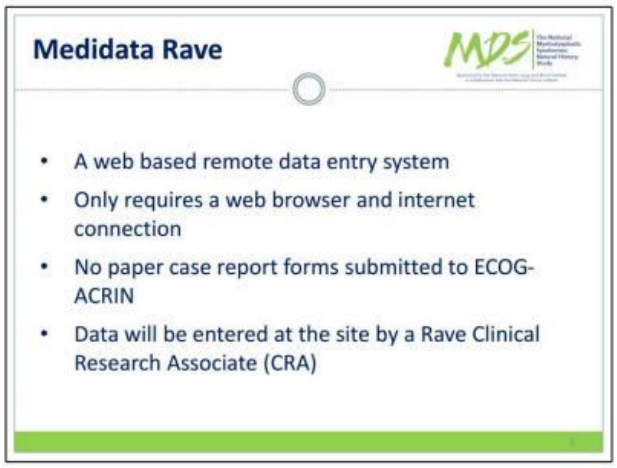
Study Chair:
Mikkael Sekeres, MD, MS
Cleveland Clinic Taussig Cancer Institute
Email: sekerem@ccf.org
Phone: 216-445-9353

Deputy Study Chair:
Steven Gore, MD
Yale Cancer Center
Email: steven.gore@yale.edu
Phone: 203-737-7013

Study Chair Liaison:
Brianna Johnson
Data and Coordinating Center (Emmes)
Email: bjohnson@emmes.com
Phone: 301-251-1161 X 17459

MEDIDATA RAVE TRAINING SLIDES

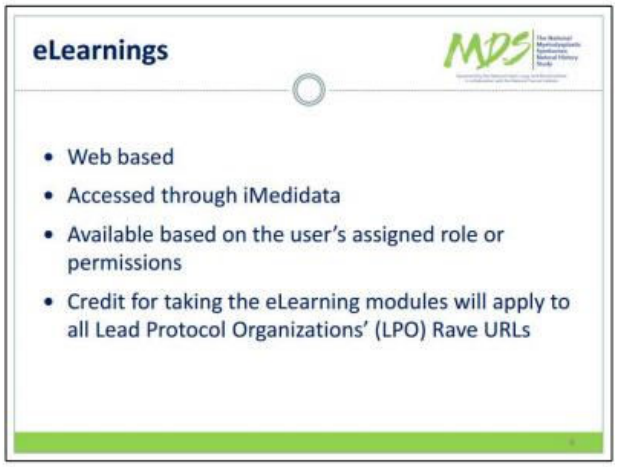

The National Myelodysplastic Syndromes Natural History Study
Introduction to Medidata Rave
Kerry Higgins, MPH
Data Management Manager
Ross Goldberg
Study Builder


Medidata Rave
A web based remote data entry system
Only requires a web browser and internet connection
No paper case report forms submitted to ECOG-ACRIN
Data will be entered at the site by a Rave Clinical Research Associate (CRA)


Sign In
medidata
Sign In
Welcome to iMedidata


Accept Invitation
medidata


Access eLearnings
medidata


eLearnings
Web based
Accessed through iMedidata
Available based on the user's assigned role or permissions
Credit for taking the eLearning modules will apply to all Lead Protocol Organizations' (LPO) Rave URLs

eLearnings

- Modules for CRAs
  - EDC Essentials for Clinical Research Coordinators**
  - ECOG-ACRIN Supplemental Training

**Medidata Clinical Research Coordinator = LPO Clinical Research Associate

**Medidata Clinical Research Associate = LPO Monitor

eLearnings

- Modules for Principal Investigators / Study Chairs
  - EDC Essentials for Investigators with Data Entry
  - ECOG-ACRIN Supplemental Training

**Medidata Clinical Research Coordinator = LPO Clinical Research Associate

**Medidata Clinical Research Associate = LPO Monitor

Access Studies



Managing Access to iMedidata

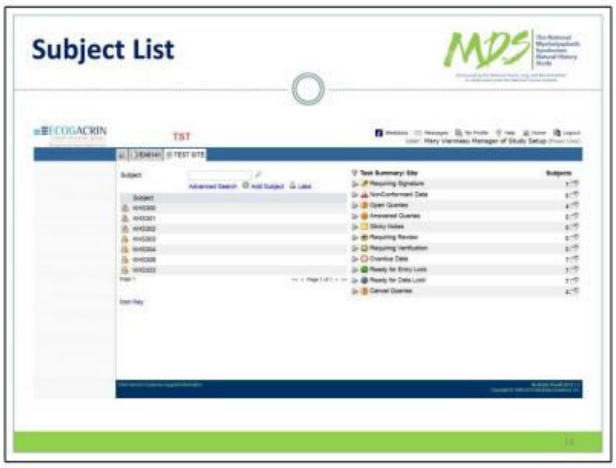
- Once site registration has been approved via the Regulatory Support System (RSS), site personnel can access iMedidata
- Access to studies can be managed two ways:
  - RSS update by Site Administrator
  - RUMS update by Site Administrator
- In both RSS and Roster Update Management System (RUMS) there is the ability to associate roles at the institution or study level

Registering a Patient

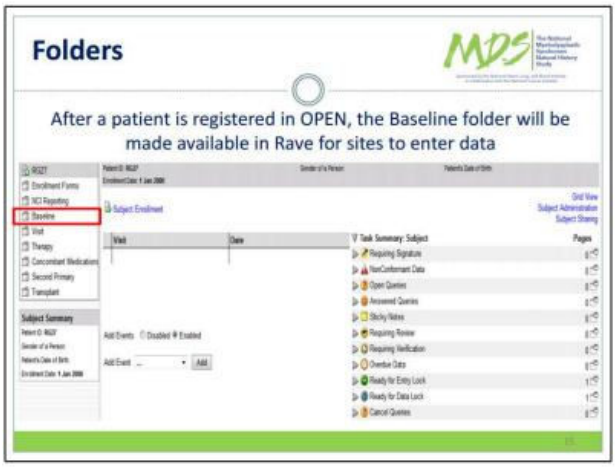
- Enrollments occur through the Oncology Patient Enrollment Network (OPEN)
- Once your patient is successfully registered, you may enter patient data in Rave

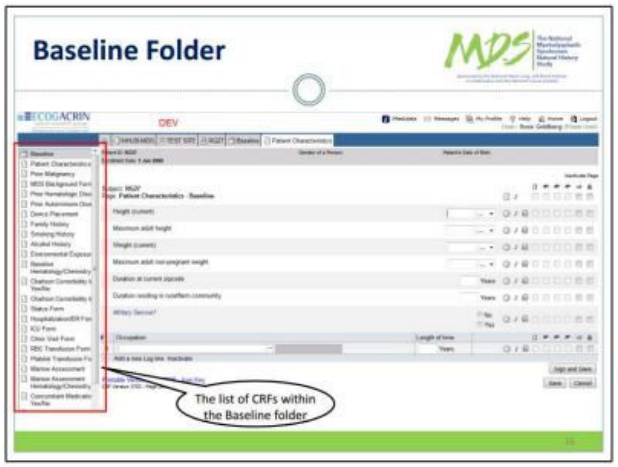
Access Rave

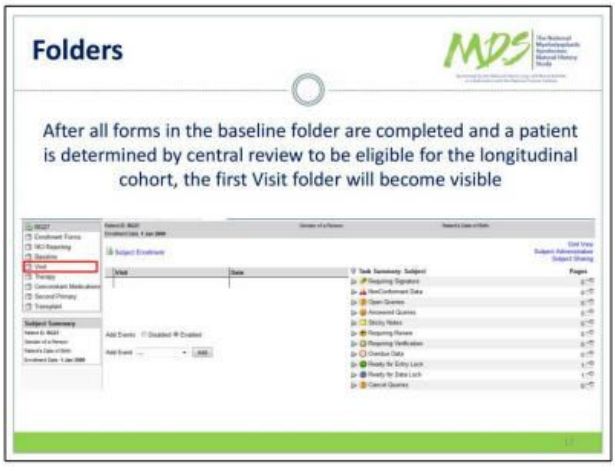


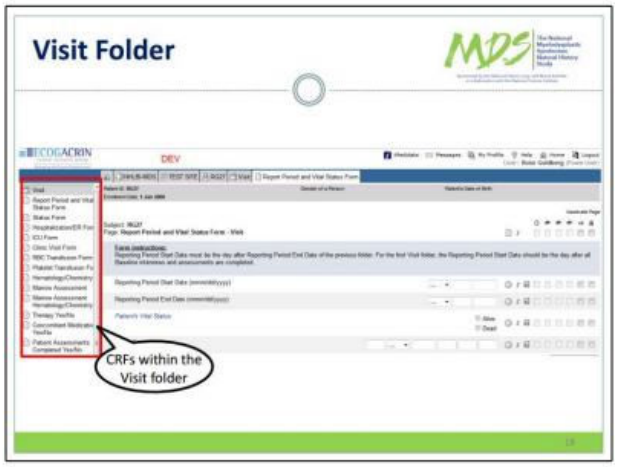

Subject List
TST


Folders
DEV
Each folder represents a timepoint or event. Folders contain CRFs


Folders
After a patient is registered in OPEN, the Baseline folder will be made available in Rave for sites to enter data


Baseline Folder
DEV
The list of CRFs within the Baseline folder

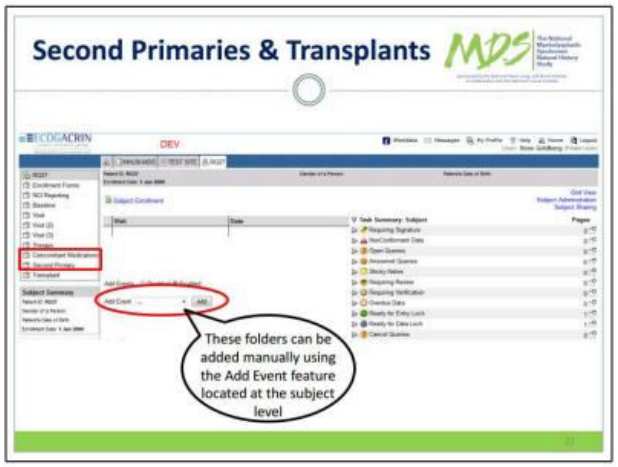

Folders
After all forms in the baseline folder are completed and a patient is determined by central review to be eligible for the longitudinal cohort, the first Visit folder will become visible

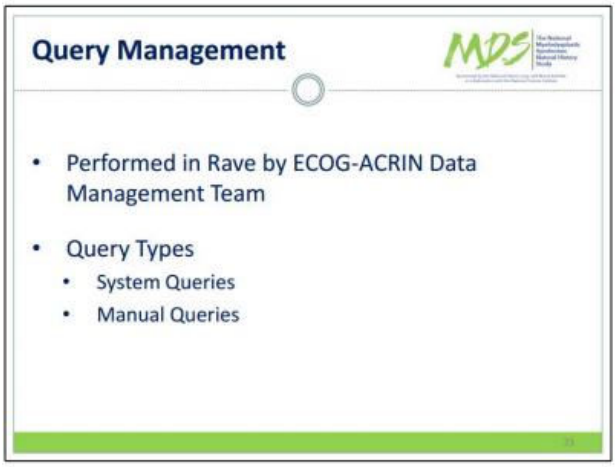

Visit Folder
DEV
CRFs within the Visit folder

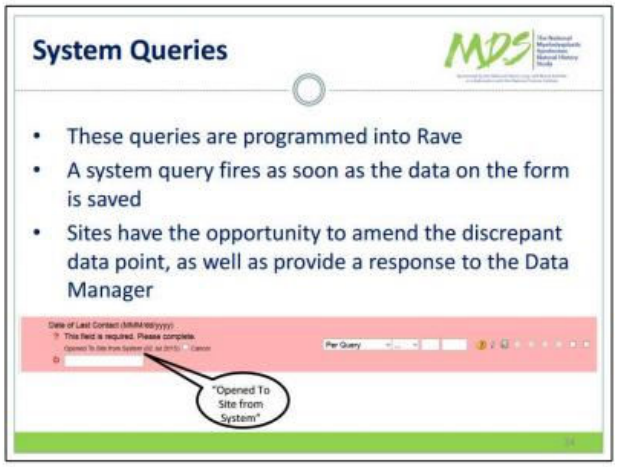

Visit Folder
The folder for the subsequent Visit will become visible after the forms in the previous Visit folder are completed.

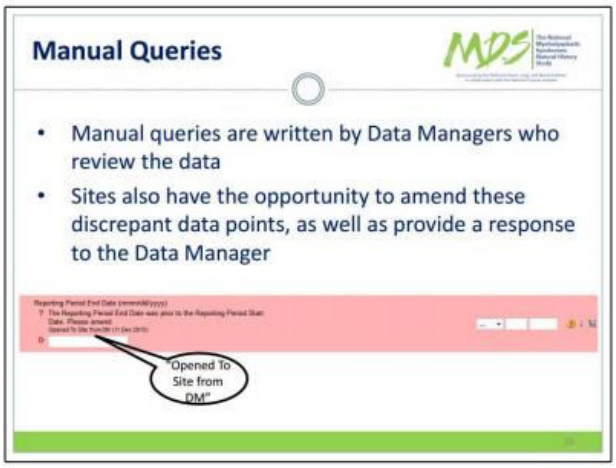

Therapy & Concomitant Medications
These folders are added by the system based on site-provided answers to trigger questions.

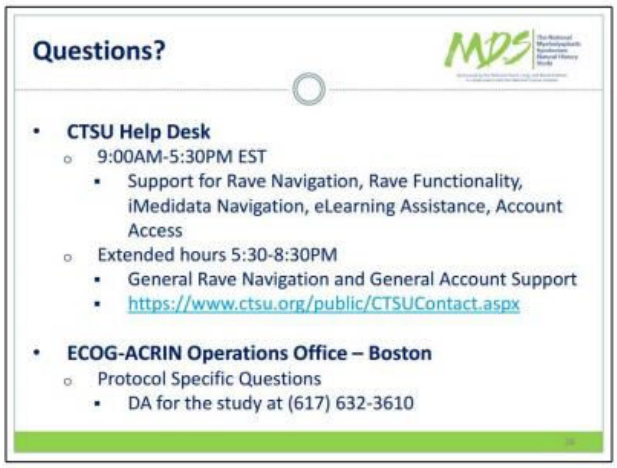

Therapy & Concomitant Medications
Trigger forms located in the Visit folder


Second Primaries & Transplants
These folders can be added manually using the Add Event feature located at the subject level


Query Management
Performed in Rave by ECOG-ACRIN Data Management Team
Query Types
System Queries
Manual Queries


System Queries
These queries are programmed into Rave
A system query fires as soon as the data on the form is saved
Sites have the opportunity to amend the discrepant data point, as well as provide a response to the Data Manager
"Opened To Site from System"


Manual Queries
MDS
Manual queries are written by Data Managers who review the data
Sites also have the opportunity to amend these discrepant data points, as well as provide a response to the Data Manager
"Opened To Site from DM"


Questions?
MDS
CTSU Help Desk
9:00AM-5:30PM EST
Support for Rave Navigation, Rave Functionality, iMedidata Navigation, eLearning Assistance, Account Access
Extended hours 5:30-8:30PM
General Rave Navigation and General Account Support
https://www.ctsu.org/public/CTSUContact.aspx
ECOG-ACRIN Operations Office – Boston
Protocol Specific Questions
DA for the study at (617) 632-3610

GLOBALTRACE TRAINING SLIDES

The National MDS Study GlobalTrace Training

For Electronic Shipping and Inventory of Specimens

1

Table of Contents

1. Logging In – Slide 3
2. Main Menu – Slides 4-6
3. Receiving Kits – Slides 7-10
4. Shipping Kits with Specimens – Slides 11-25
5. Electronically Rejected Shipments – Slides 26-27
6. Expired Kits – Slides 28
7. Additional Utilities – Slides 29-37
   - Kit inventory – Slides 29-30
   - Shipment Summary – Slides 31-33
   - Modifying Shipments – Slides 34-36
   - Deleting Shipments – Slide 37
8. Summary – Slide 38
9. Contact Information – Slide 39

2

Logging In

- After completing the training, email the contact below to request a username and temporary password to access GlobalTrace℠.

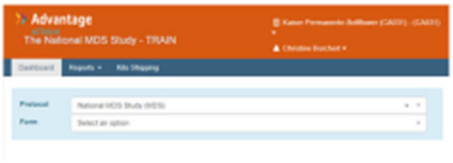
  Data Manager/Clinical Study Manager at the Data Coordinating Center Email: mdscontact@emmes.com

- To log in, enter your username and password at https://emmes.okta.com/login/login.htm
- When you log in for the first time, you will be prompted to create an account and agree to the Electronic Signature Agreement.

3

Main Menu

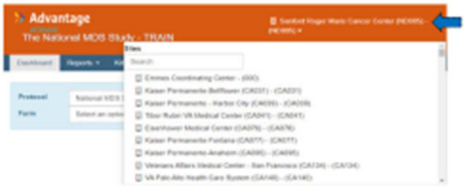
- After logging in, the *Dashboard* screen appears.
- From the *Dashboard*, users can navigate to the appropriate page to Receive Kits, Ship Kits, and check your site's kit inventory.



4

Main Menu

- If you have access to multiple sites, change sites in the data system by navigating to the top right corner of the header.
- Select the site from the drop-down menu and click *Select*.
- The site name appears in the upper right corner.



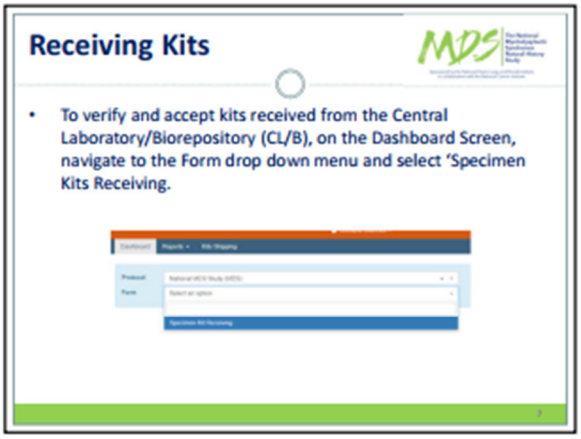
5

Main Menu

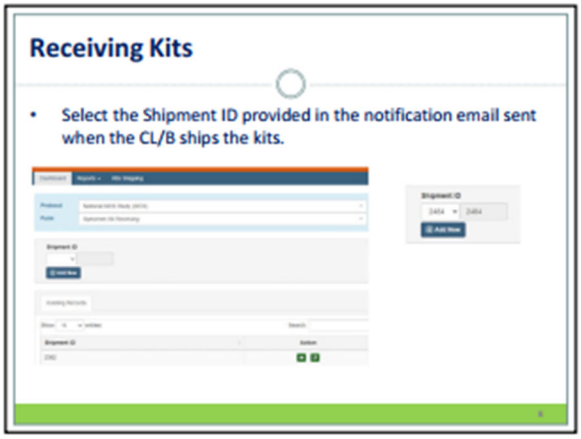
- The date and time appear in the bottom right corner of the screen.
  - The system will automatically log out after 20 minutes of inactivity.
  - To prevent the automatic log-out, click *Stay Connected* when the pop-up appears.



6


Receiving Kits
To verify and accept kits received from the Central Laboratory/Biorepository (CL/B), on the Dashboard Screen, navigate to the Form drop down menu and select 'Specimen Kits Receiving.

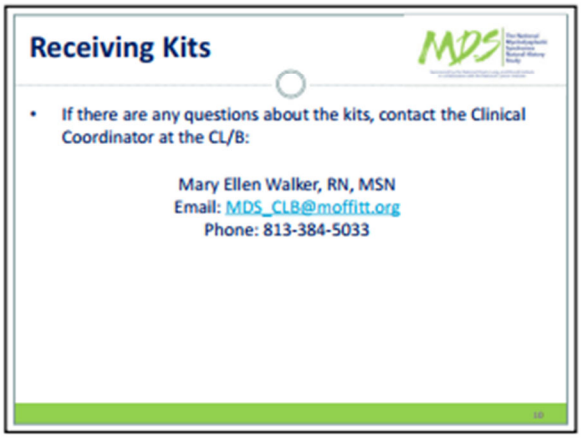
7


Receiving Kits
Select the Shipment ID provided in the notification email sent when the CL/B ships the kits.

8


Receiving Kits
The Specimen Kit Receiving Form opens as shown below.
Complete the form and click Save.

9


Receiving Kits
If there are any questions about the kits, contact the Clinical Coordinator at the CL/B:
Mary Ellen Walker, RN, MSN
Email: MDS_CLB@moffitt.org
Phone: 813-384-5033

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Shipping Kits with Specimens
On the Dashboard screen, click Kits Shipping to electronically track the shipment of used specimen collection kits from your site to the CL/B.

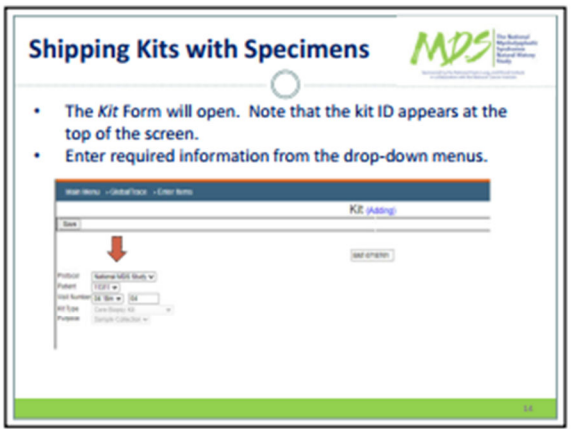
11


Shipping Kits with Specimens
The GlobalTrace menu will appear.
Kits must be added to create the electronic shipment.
Click Add.
GlobalTrace

12



13



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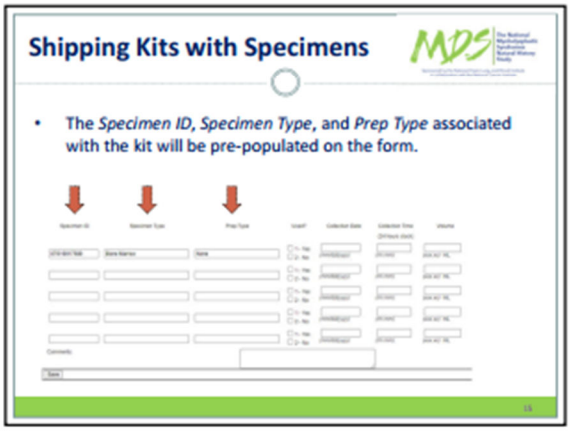

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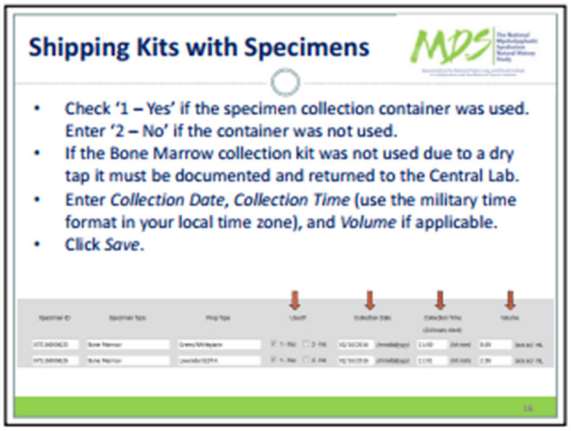

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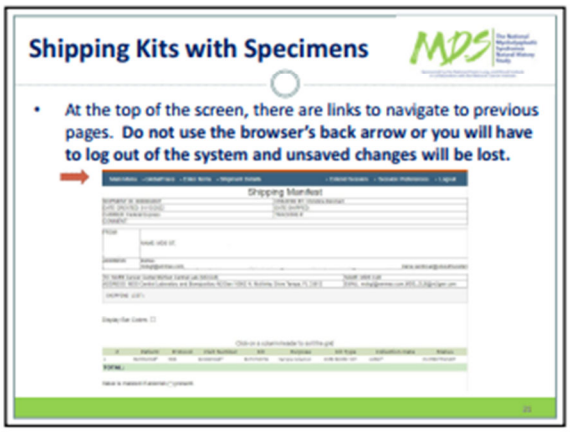

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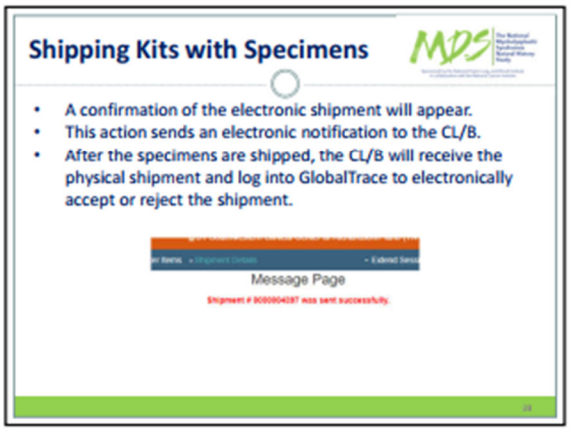

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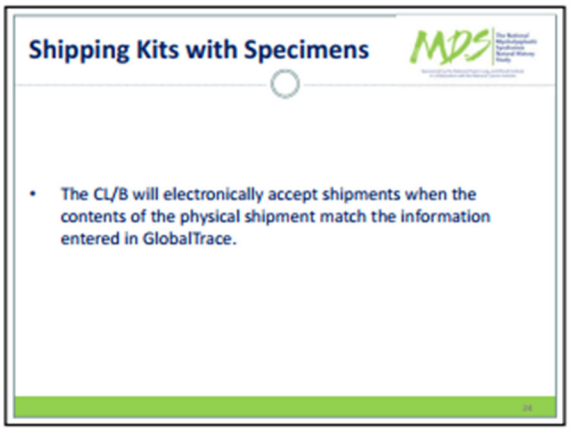

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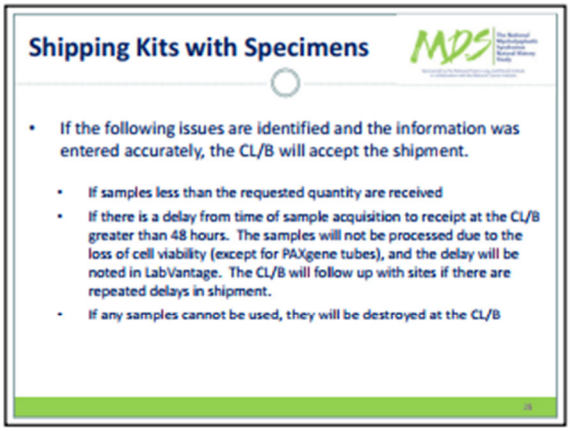

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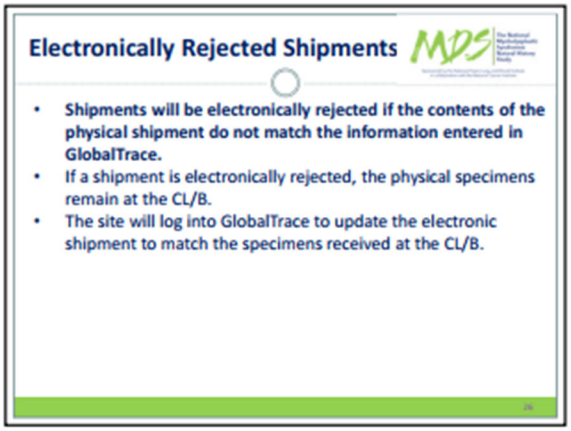

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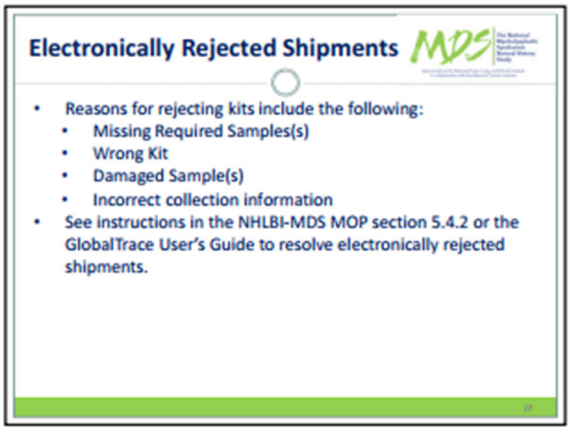

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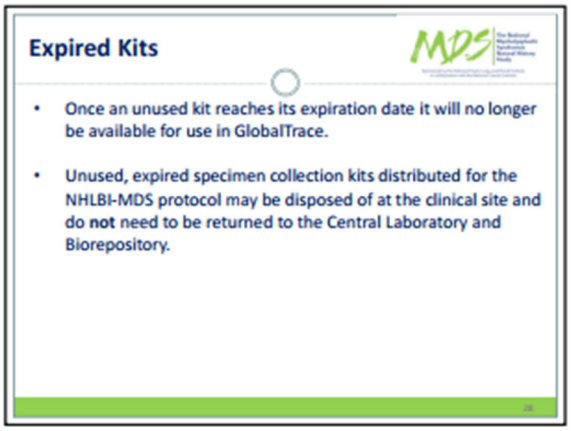

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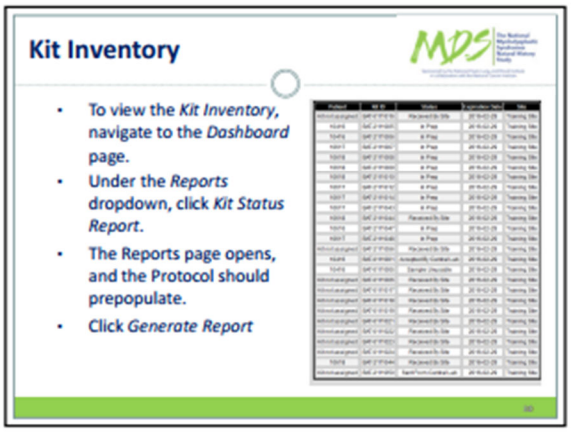

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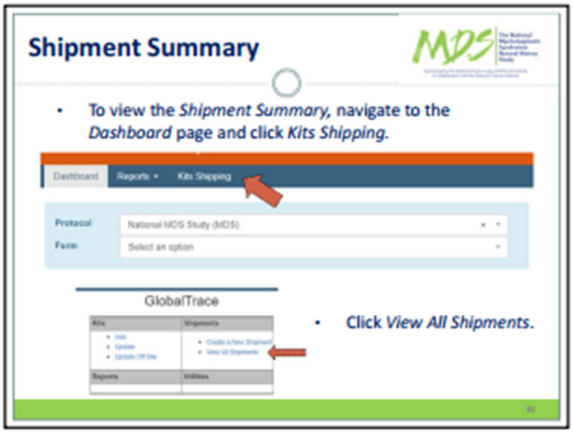

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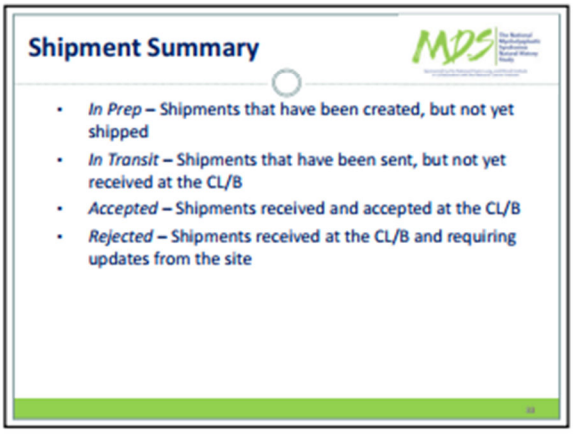

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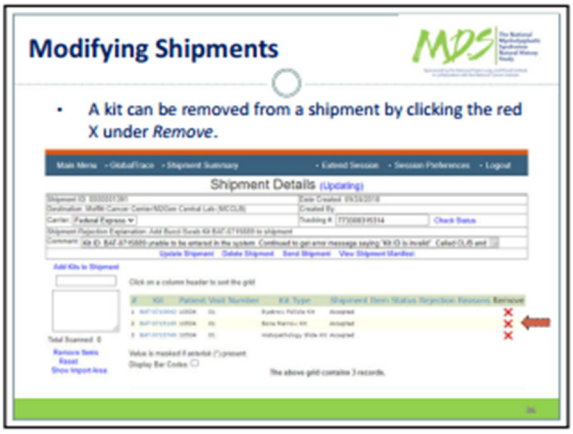

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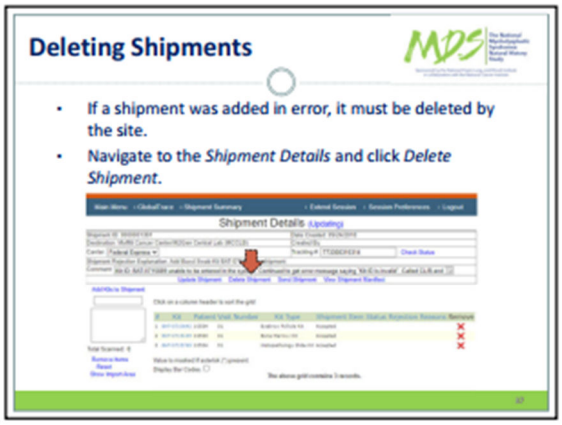
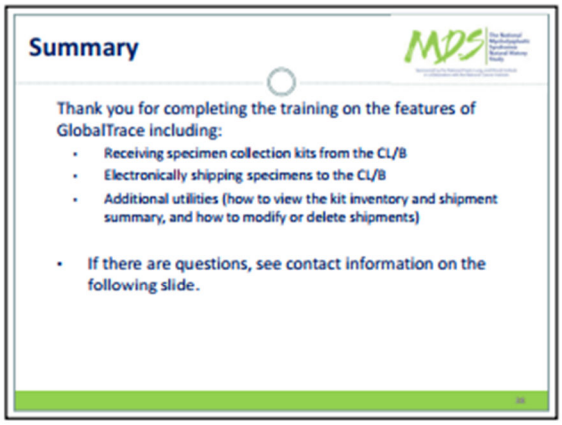

Deleting Shipments
If a shipment was added in error, it must be deleted by the site.
Navigate to the Shipment Details and click Delete Shipment.
Shipment Details

37


Summary
Thank you for completing the training on the features of GlobalTrace including:
Receiving specimen collection kits from the CL/B
Electronically shipping specimens to the CL/B
Additional utilities (how to view the kit inventory and shipment summary, and how to modify or delete shipments)
If there are questions, see contact information on the following slide.

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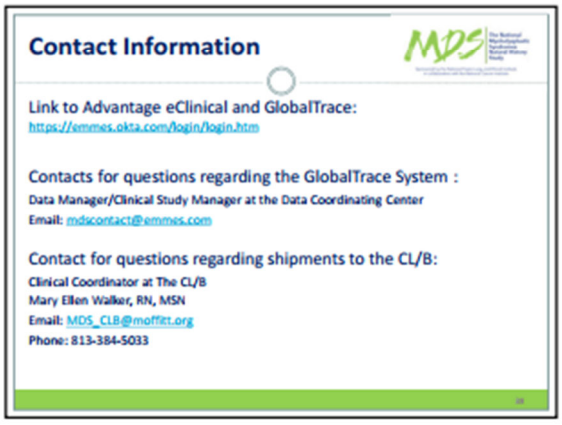
Contact Information
Link to Advantage eClinical and GlobalTrace:
https://emmes.okta.com/login/login.htm
Contacts for questions regarding the GlobalTrace System :
Data Manager/Clinical Study Manager at the Data Coordinating Center
Email: mdscontact@emmes.com
Contact for questions regarding shipments to the CL/B:
Clinical Coordinator at The CL/B
Mary Ellen Walker, RN, MSN
Email: MDS_CLB@moffitt.org
Phone: 813-384-5033

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BIOSPECIMEN ACQUISITION TRAINING SLIDES

The National Myelodysplastic Syndromes Natural History Study

Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

Biospecimen Acquisition Training Module

The National MDS Protocol

Presented by the:
Central Laboratory and Biorepository (CL/B)
Moffitt Cancer Center/M2Gen, Tampa, FL

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Slide 7:	Manual of Procedures
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Slide 10:	Shipping Requirement
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Slide 12:	Overview of Biospecimen Handling
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Slide 17:	Register Participant

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Slide 38-40:	Contact Slides, Additional Information, Conclusion of Training

Abbreviations

BM:	Bone Marrow
CL/B:	Clinical Laboratory and Biorepository, Moffitt Cancer Center/M2Gen
CTSU:	NCI Cancer Trials Support Unit
DCC:	Data Coordinating Center, Emmes Corporation
GT:	GlobalTrace, electronic shipping program
H&E:	Hematoxylin and Eosin
LIMS:	Laboratory Information Management System, LabVantage is used at the CL/B for this purpose
MOP:	Manual of Procedures
PB Samples:	Peripheral Blood Samples
PBMC's:	Peripheral Blood Mononuclear Cells
QC:	Quality Control
W/G:	Wright-Giemsa Stain

General Overview of Biospecimen Acquisition

Training Information

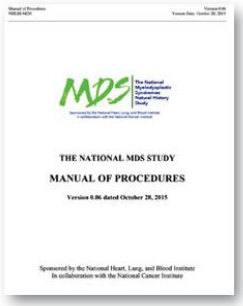
Required training will be available through the web-based learning management platform, Mindflash

For information regarding Sample Acquisition and Shipping view the following training modules:

1. GlobalTrace
2. Biospecimen Acquisition
3. Biospecimen Shipping

Manual of Procedures

1. Operational details appear in the "Manual of Procedures" (MOP)
2. Section 8 of the MOP provides information regarding the collection and shipping of biologic materials for this protocol
3. Current MOP version is available on the CTSU study website


THE NATIONAL MDS STUDY

MANUAL OF PROCEDURES

Version 8.06 dated October 28, 2015

Sponsored by the National Heart, Lung, and Blood Institute
In collaboration with the National Cancer Institute

Shipping Address

1. Sample processing and storage will take place at the Central Laboratory and Biorepository (CL/B)
2. The CL/B is located at M2Gen, Corporation, which is associated with the Moffitt Cancer Center & Research Institute in Tampa, FL.
3. All samples collected for this protocol will be shipped to:

MDS Central Laboratory & Biorepository
M2Gen
10902 N. McKinley Drive
Tampa, FL 33612
ATTN: Jeff Painter
Ph: 813-745-6726



NOTE: Do Not Ship Samples to Moffitt Cancer Center

Contacts at the CL/B

The Central Laboratory and Biorepository (CL/B) will assist in identifying any challenges a clinical team may have in operationalizing the protocol and performing the required sample collection procedures.

For questions or assistance please contact:

Mary Ellen Walker, RN, MSN
CL/B Clinical Coordinator at 813-384-5033
Mary.Walker@m2gen.com

OR

Jeffrey S. Painter, BS
CL/B Biorepository Specialist at 813-745-6726
Jeff.Painter@Moffitt.org

Shipping Requirement

1. Sample tracking will occur using GlobalTrace
2. View the "GlobalTrace Training Module" for electronic shipping and inventory instructions
3. Multiple shipments may be necessary
4. CL/B will provide FedEx account number once required registration documents are received and all required training is completed

Personnel Requirement

To participate in this protocol a study site must comply with the following regulations:

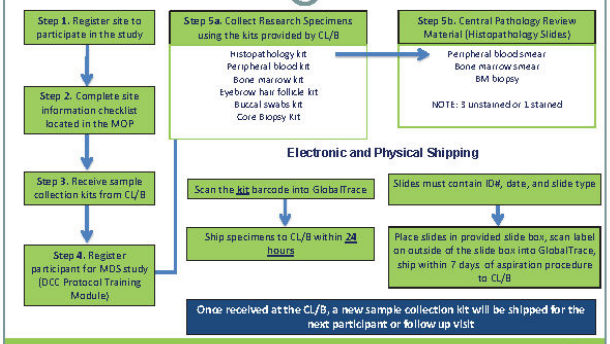


- *United States Department of Transportation* (DOT)
- *International Air Transport Association* (IATA) Dangerous Goods Regulations

A member of the study staff must be certified with "IATA Training" to ship biologic substances

***NOTE:** If IATA training is needed, please contact the CL/B Clinical Coordinator for assistance*

Overview of Biospecimen Handling



Site Registration/Checklist

Step 1. Register site to participate in the study

1. Regulatory requirements will be overseen by the NCI Cancer Trials Support Unit (CTSU)
2. "The National MDS Study: Site Information Checklist" provides important information to the CL/B about your site
3. Complete this checklist as instructed by the CTSU and they will forward the document to the CL/B.

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Site Registration/Checklist

Step 2. Complete the CL/B Site Information Checklist located on the ECOG/ACRIN Website

1-D barcode



Barcode Scanner



The Site Information Checklist assists with operations and planning. The checklist will collect the following information:

- Information related to biospecimen handling and shipping
- Information regarding staff shipping qualifications
- Anticipated number of participants in 6 months for kit distribution
- Mechanism for collection of pathology slides
- Sites will need access to a 1-D bar code scanner. The site should request a barcode scanner on the Site Information Checklist if they do not have access to one.

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Receiving Kits from CL/B

Specimen collection kits come from CL/B

Step 3. Receive specimen collection kits from CL/B

1. Kits from the CL/B contain all necessary materials for sample collection and shipping
2. Each "KIT" has a 1-D barcode on the outside of the package to aide in tracking*
3. Once kits are received, verify the content list in GlobalTrace (see GlobalTrace training)
4. Contact the CL/B if the package is damaged

*Note: a 2-D barcode scanner can be used to read a 1-D barcode

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Types of Kits



Multiple types of specimen collection kits will be sent from the CL/B prior to enrolling participants

1. Open the FedEx Pak
2. Six types of kits will be present

Peripheral Blood Kit
Bone Marrow Kit
Histopathology Slide Kit
Buccal Cell Collection Kit
Eyebrow Hair Follicle Kit
Bone Marrow Core Biopsy Slide Kit

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Register Participant

Step 4. Register participant for MDS study (Protocol Training Module)

Follow instructions in the "Protocol Training Module" to register participant in the MDS study



You are now ready to collect samples!

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Detailed Instruction for

Biospecimen Acquisition

18

Summary of Kits

Step 5. Collect Research Specimens using the kits provided by CL/B

Peripheral blood kit
Bone marrow kit
Eyebrow hair follicle kit
Buccal swabs kit
Histopathology kit
Bone Marrow Biopsy Slide kit

It is possible all biologic material will be collected during the first visit, but multiple sample shipments may be necessary. Samples must be received in the lab within 24 hours to preserve viability.

If samples are collected on Friday, please ship for Saturday delivery.

Extra shipping supplies are provided in your material from the CL/B

Germline Control

Multiple somatic mutations have been identified in MDS. For accurate genetic description and assignment, non-hematopoietic contaminated germline DNA is required as a control.

For this protocol, germline control biospecimens will be collected for future genomic studies:

1. Eyebrow hair follicle DNA; NOTE: Hair from the hairline may be submitted instead of or as a supplement to the eyebrow hair. The follicle must be obtained
2. Buccal cell DNA



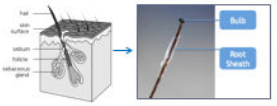
DNA

Eyebrow Hair Follicle Collection

1. Select the *Eyebrow Hair Follicle Collection Kit*-
   - **NOTE:** Sample collection instructions will be included in each kit.
2. Explain the procedure to the participant
3. The participant may elect to obtain the eyebrow sample themselves or request assistance from approved study personnel*

What should be collected.....

6 eyebrow hairs per brow (12 total)



Eyebrow hair follicle (bulb) contains high quality genomic DNA without blood contamination

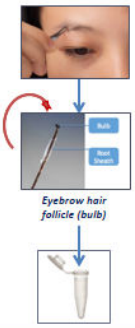
**For consistency purposes, the preference is for the study coordinator to collect this sample*

Eyebrow Hair Follicle Collection

How to collect the specimen.....

1. Position the participant near a window with natural light or under a bright light with a mirror
2. Brush brows up and out with fingers
3. Tweeze hairs in the direction they grow
4. Grab one hair at a time and hold skin taut when plucking. It is critical that the hair follicle is attached to the hair shaft
5. Use sterile tweezers to place each eyebrow hair in the sterile tube provided
6. Repeat steps 4 and 5 until six hairs from each eyebrow are added to the tube; Hair from the hairline may be submitted instead of or as a supplement to the eyebrow hair. The follicle must be obtained
7. Close tube tightly

***NOTE:** This tube contains no liquid preservative.*



Eyebrow hair follicle (bulb)

Eyebrow Hair Follicle Collection

Ensure that the sample can be tracked correctly....

1. Place the collection tube with eyebrow hairs into the biohazard bag (Use the bag from the "Eyebrow Hair Follicle Kit" because it is linked to the eyebrow hair tube)
2. Ensure that that the participant ID is linked appropriately within GlobalTrace when the sample is ready to be shipped
3. Refer to the "Biospecimen Shipping Slides" for complete shipping details

Ship sample on the day of collection for receipt at the CL/B within 24 hours; If samples are collected on Friday, please select Saturday Delivery!

Place tube back into the original barcoded bag!!!

Eyebrow Hair Follicle Kit



Buccal Swab Procedure

1. Use the Buccal Swab Collection Kit provided by the CL/B.
   - ***Note:** sample collection instructions are provided in each sample collection kit*
2. This kit contains two sterile cotton swabs, which are each contained inside sterile packaging
3. Inside the sterile packing, there is a plastic transport tube called the "culturette". One is provided for each cheek (as shown)
4. The kit ID number is located on the outside of the red biohazard bag. This will be used for sample tracking.



Buccal Cells



Buccal Swab Procedure

How to collect the specimen.....

1. Explain the procedure to the participant
2. Instruct the participant to not eat or drink 30-60 minutes prior to collection
3. After the waiting period, rinse mouth for 20 seconds with water and expectorate the rinse
4. Remove one cotton swab from the sterile culturette tube
5. To swab inner cheek, insert the swab into the mouth between the inside of the cheek and the upper gum line. Press firmly and twirl the brush against the inside of the inner cheek using an up and down motion from front to back and back to front. Cover as much cheek area as possible.
6. Allow swab to air dry 1 minute before placing back into the sterile plastic culturette container
7. Repeat steps 3, 4, and 5 with second cotton swab on opposite cheek





Buccal Swab Procedure

1. Affix barcode labels provided in the kit on both culturette containers
2. Place both culturette containers back into the biohazard bag (Use the bag from the "Buccal Swab Kit" because it is linked to the culturette containers)
3. Ensure the participant ID is linked appropriately within GlobalTrace
4. Refer to the "Biospecimen Shipping Slides" for complete shipping details

Ship sample on the day of collection for receipt at the CL/B within 24 hours; If samples are collected on Friday, please select Saturday Delivery!



Peripheral Blood Collection

What should be collected.....

Collection procedure should follow institutional guidelines:

1. Select the Peripheral Blood Collection Kit
   - **NOTE:** Sample collection instructions will be provided in each sample collection kit
2. A bar code label is located on the outside of each kit to help with tracking
3. 34.2 mL of blood is required at each sampling point. **Collect blood in the following order:**
   - 3 mL in red top tube (serum)
   - Two 10 mL green top (heparinized) tubes (total of 20 mL's)
   - 8.7 mL in PAXgene DNA tube
   - 2.5 mL in PAXgene RNA tube



Special Handling Procedures for Peripheral Blood

1. Allow all blood tubes to fill to maximum capacity
2. Draw the PAXgene RNA tube last during the phlebotomy procedure
   - After blood collection, gently invert the PAXgene blood RNA and PAXgene DNA tubes 8 to 10 times
   - Store the PAXgene blood RNA and PAXgene DNA tubes upright at room temperature until shipped
3. Return ALL blood collection tubes included in the peripheral blood collection kit to the CL/B; Remember to record the volume collected in each tube (even if 0) in GlobalTrace

Special Handling Procedures for Peripheral Blood

1. Place samples in the transport sleeve to prevent breakage
2. Roll up the sleeve and return to the red biohazard bag (Use the bag from the "Peripheral Blood Kit" because it is linked to the specimen)
3. Ensure the participant ID is linked appropriately within GlobalTrace when the sample is ready to be shipped
4. Place the biohazard bag with the blood tubes into the plastic transport canister (as shown), close tightly
5. Refer to the "Biospecimen Shipping Slides" for complete shipping details

Ship sample on the day of collection for receipt at the CL/B within 24 hours; If samples are collected on Friday, please select Saturday Delivery!



Place tube in original container with barcode

Bone Marrow Collection

What should be collected.....

Procedures should follow institutional guidelines:

1. Select the Bone Marrow Collection Kit
   - **NOTE:** Sample collection instructions will be provided in each sample collection kit
2. A barcode is located on the outside of each kit to help in tracking
3. Bone marrow samples are required at study entry and every time a bone marrow sample is obtained for clinical care. Collection is stopped after AML diagnosis
4. Bone marrow assessments will ONLY be conducted as part of routine clinical care

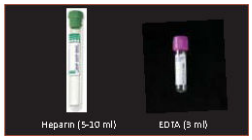


Bone Marrow Collection (continued)

Procedure should follow institutional guidelines:

13 mL of bone marrow aspirate is required at each sampling point

1. Invert tubes with bone marrow samples as quickly as possible to prevent clot formation
2. Please collect bone marrow samples in the following order:
   - 5-10 mL in green top (heparinized) tube (see NOTE)
   - 3 ml tube containing EDTA



***NOTE:** 10 mL is preferential if IRB approval is received*

Special Handling Procedures for Bone Marrow

1. Place both tubes containing bone marrow aspirate into the absorbent transport sleeve
2. Roll up the sleeve and return to the red biohazard bag (Use the bag from the "Bone Marrow Kit" because it is linked to the biospecimen) and close tightly
3. Ensure the participant ID is scanned and linked appropriately within GlobalTrace when the sample is ready to be shipped
4. Place the biohazard bag with the bone marrow tubes into the plastic transport canister (as shown), close tightly
5. Refer to the "Biospecimen Shipping Slides" for complete shipping details



Ship sample on the day of collection for receipt at the CL/B within 24 hours; If samples are collected on Friday, select Saturday Delivery!

Place tubes in original container with barcode

Central Pathology Review- BM Bx

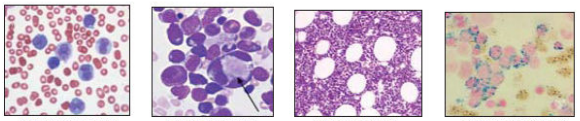
1. For uniform participant classification across multiple sites, Central Pathology Review will be conducted at the CL/B under guidance of highly trained clinical hematopathologists
2. The World Health Organization (WHO) defined MDS categories should be recorded based on the local clinical assessment. The Central Pathology Review process will not be conducted until this local data is recorded in Medidata Rave
3. Bone Marrow Core Biopsy slides from the baseline visit **must** be submitted for review
4. Submission of slides for Central Pathology Review is mandatory and must be submitted within 7 days of the aspiration procedure
5. Failure to submit pathology slides will render the case unevaluable

Central Review Material

Summary of slides required for Central Pathology Review

Pathology Material Required for Central Review						
		Unstained	Wright Giemsa	Prussian Blue (Iron)	H&E
Peripheral Blood	required	3 slides			
	Optional*		1 slide		
Bone Marrow Aspirate	Required	3 slides			
	Optional*		1 slide	1 slide	
Bone Marrow Core Biopsy	Required	1 slide			1 slide

*Note: submission of optional stained slide is preferred



W/G Peripheral Blood | *W/G Bone Marrow* | *H&E Bone Marrow* | *Prussian Blue Stain BM*

Histopathology Slides

1. Select the Histopathology Slide Collection Kit
   NOTE: Sample collection instructions will be provided in each sample collection kit
2. A barcode label is located on the outside of the slide box and on the biohazard bag to help with tracking
3. The barcode should be scanned into GlobalTrace and it will populate within the electronic system
4. Please work with your local pathology group to ensure that extra peripheral blood and bone marrow slides are prepared for this study
5. The pathology group should label slides with case number, date of preparation, and tissue/stain type
6. Place the slides into the slide box provided; Refer to the "Biospecimen Shipping Slides" for complete shipping details

Trouble-Shooting

1. Contact the CL/B with any question or concern that arises during the sample acquisition and shipping procedures.
2. Contact the CL/B if there is a broken tube or damage to the kit.
3. If a participant is present at the site and a collection tube breaks or is unusable, it may be replaced with one from the site if available.
4. If the appropriate replacement tube is not available, a tube from another MDS biospecimen collection kit may be used. Scan the replacement kit ID into GlobalTrace to populate the tubes. Include all unused tubes from the replacement kit with shipment and indicate zero volume in GlobalTrace.
5. Check each kit and tube listed in GlobalTrace carefully before shipping to the CL/B. Primary tracking occurs at the "kit" level. The original packaging should be returned exactly as delivered from the CL/B.
6. If the tubes do not match the "kit ID", then the shipment will be rejected in GT and every effort will be made to correct the inconsistency.

Participant Withdrawal

Depending on clinical site and study-specific requirements for sample and data retention, the CL/B will:

1. Maintain current specimens and annotate withdrawal status
2. At the request of the participant, specimens stored at the CL/B will be properly disposed

Contacts at the CL/B

The Central Laboratory and Biorepository (CL/B) will assist in identifying any challenges a clinical team may have in operationalizing the protocol and performing the required sample collection procedures.

For questions or assistance please contact:

Mary Ellen Walker, RN, MSN
CL/B Clinical Coordinator at 813-384-5033
Mary.Walker@m2gen.com

OR

Jeffrey S. Painter, BS
CL/B Biorepository Specialist at 813-745-6726
Jeff.Painter@Moffitt.org

Links and Contact Information

Optional Training Materials:

1. IATA Training:
   - http://www.iata.org/training/courses/Pages/index.aspx
   - http://www.fedex.com/us/services/pdf/HazmatShippingGuide.pdf
2. Study Website:
   - https://thenationalmdsstudy.net/
3. MDS Classification: International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3):
   - http://www.who.int/classifications/icd/adaptations/oncology/en/

CL/B PI:
PK Epling-Burnette, PharmD, PhD
Moffitt Cancer Center
Email: Pearlie.Burnette@moffitt.org
Phone: 813-745-6177

Study Chair:
Mikkael Sekeres, MD, MS
Cleveland Clinic Taussig Cancer Institute
Phone: (216) 445-9353

Study Chair Liaison:
Brianna Johnson
The Emmes Corporation
Email: bjohnson@emmes.com
Phone: (301)251-1161 x17459

The National Myelodysplastic Syndromes Natural History Study
Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

This Concludes Your Training Manual for Biospecimen Collection

THANK YOU!

Presented by the:
Central Laboratory and Biorepository (CL/B)
Moffitt Cancer Center/M2Gen, Tampa, FL

BIOSPECIMEN SHIPPING TRAINING SLIDES

The National Myelodysplastic Syndromes Natural History Study

Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

Biospecimen Shipping Training Module

The National MDS Study

Presented by the:
Central Laboratory and Biorepository (CL/B)
Moffitt Cancer Center/M2Gen, Tampa, FL

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Abbreviations

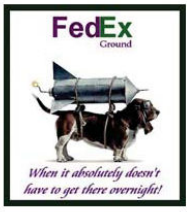
BM:	Bone Marrow
CL/B:	Clinical Laboratory and Biorepository, Moffitt Cancer Center/M2Gen
CTSU:	NCI Cancer Trials Support Unit
DCC:	Data Coordinating Center, Emmes Corporation
GT:	GlobalTrace, electronic shipping program
H&E:	Hematoxylin and Eosin
LIMS:	Laboratory Information Management System, LabVantage is used at the CL/B for this purpose
MOP:	Manual of Procedures
PB Samples:	Peripheral Blood Samples
PBMC's:	Peripheral Blood Mononuclear Cells
QC:	Quality Control
W/G:	Wright-Giemsa Stain

Training Information

Slides For Coordinators or Personnel Certified to Ship Biological Material

Samples are now ready to ship!!!





Training Information

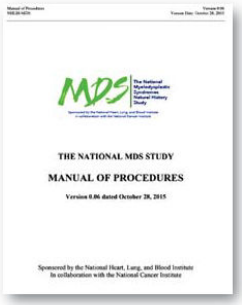
Required training will be available through the web-based learning management platform, Mindflash

For information regarding Acquisition and Electronic Shipping view the following training modules:

1. GlobalTrace
2. Biospecimen Acquisition
3. Biospecimen Shipping

Manual of Procedures

1. Operational details appear in the "Manual of Procedures" (MOP)
2. Section 8 of the MOP provides information regarding the shipping of biologic materials for this protocol
3. Current MOP version is available on the CTSU study website



Shipping Requirements

1. Sample tracking will occur using GlobalTrace
2. View the "GlobalTrace Training Module" for electronic shipping and inventory instructions
3. Multiple shipments may be necessary
4. CL/B will provide FedEx account number once required registration documents are received and all required training is completed

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Personnel Requirement

To participate in this protocol a study site must comply with the following regulations:



- *United States Department of Transportation* (DOT)
- *International Air Transport Association* (IATA) Dangerous Goods Regulations

A member of the study staff must be certified with "IATA Training" to ship biologic substances

NOTE: *If IATA training is needed, please contact the CL/B Clinical Coordinator for assistance*

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Shipping Overview

1. Multiple types of samples and materials are required for this study, which are summarized in the Sample Acquisition Training Module
2. Detailed information on specimen shipping can be found in the MOP and in the "GlobalTrace Training" module
3. Sample collection for a single visit type (baseline or follow up) may occur on the same day or on different days
4. Pathology material generated by the pathologist may be shipped at a later time

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Shipping Material

1. The CL/B will provide specimen collections kits and extra shipping material for each participant so multiple shipments are possible.
2. Biospecimen collection, bar code scanning and shipping are all critical elements for the success of this project!

1-D barcode



Barcode Scanner



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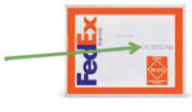
Key Shipping Procedures

1. Barcodes will be present on the outside "kit" and on the tubes when materials are sent from the CL/B
2. The "kit" ID barcode should be scanned into GlobalTrace and it will populate the tubes (ie, specimens) within the electronic system
3. Send biospecimens back in the ***original*** packaging!!!
4. Ensure all tubes in the bag match those populated in GlobalTrace for that kit
5. For each kit, create a sample manifest in GlobalTrace, place a copy **INSIDE** the FedEx UN3373-pak, and return to the CL/B!!!





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Step by Step Packaging Instructions

Next, you will be presented with step by step shipping instructions for the following kits……

Liquids:
Peripheral blood kit
Bone marrow kit

Solids:
Eyebrow hair follicle kit
Buccal swabs kit
Histopathology kits



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Category B – Packaging Liquids

Category B Requirements

- Level 1. Primary watertight inner receptacle
- Level 2. Absorbent material
- Level 3. Secondary watertight inner receptacle
- Level 4. Sturdy outer packaging for MDS kit
- Level 5. FedEx Overpack 3373 or box



Shipping Peripheral Blood

Step 1: Ensure all peripheral blood tubes have been collected (5 total)

Step 2: Place tubes in absorbent sleeve. This acts to cushion tubes and protect from spills

Step 3: Roll up absorbent sleeve and place into biohazard bag labeled "peripheral blood kit". Close tightly

Step 4: Scan "kit ID" into GlobalTrace



Step 5: Roll up biohazard bag and place into large hard outer canister. Close top carefully

Step 6: Place hard outer canister with PB kit into FedEx Overpack 3373 (bag) with shipping manifest.

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Category B – Packaging Liquids

Category B Requirements

- Level 1. Primary watertight inner receptacle
- Level 2. Absorbent material
- Level 3. Secondary watertight inner receptacle
- Level 4. Sturdy outer packaging for MDS kit
- Level 5. FedEx Overpack 3373 or box



Shipping Bone Marrow

Step 1: Ensure all bone marrow tubes have been collected (2 total)

Step 2: Place tubes in absorbent sleeve. This acts to cushion tubes and protect from spills

Step 3: Roll up absorbent sleeve and place into biohazard bag labeled "bone marrow kit". Close tightly

Step 4: Scan "kit ID" into GlobalTrace



Step 5: Roll up biohazard bag and place into small hard outer canister. Close top carefully

Step 6: Place hard outer canister with BM kit into FedEx Overpack 3373 (bag) with shipping manifest.

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Category B – Packaging Eyebrow Hairs

Packaging of Biospecimens without Liquid

Eyebrow Hairs



Step 1: Ensure eyebrow hairs are contained in tube

Step 2: Place tube into original biohazard bag labeled "eyebrow hair kit"

Step 3: Scan "kit ID" into GlobalTrace



Step 4: Place "eyebrow hair kit" directly into FedEx Overpack 3373 (bag) with shipping manifest.

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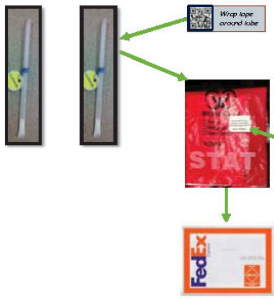
Category B – Packaging Buccal Swabs

Packaging of Biospecimens without Liquid



Step 1: Ensure plastic culturette containers contain swabs and have been labeled with bar codes!!!!

Step 2: Place bar code labeled culturette tubes (2 total) into original biohazard bag labeled "buccal swab kit"

Step 3: Scan "kit ID" into GlobalTrace



Step 4: Place "buccal swab kit" directly into FedEx Overpack 3373 (bag) with shipping manifest.

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Shipping Histopathology Slides

1. Please work with your local pathology group to ensure extra peripheral blood and bone marrow slides are prepared for this study.
2. The slide box has a barcode on the outside for tracking. The barcode on the slide box must match the barcode on the biohazard bag. Each slide must be manually labeled as described in Biospecimen Acquisition Training Module.
3. To prevent slides from breaking, use the proper transport container (such as a padded envelope) or add sufficient packing material to make sure the slides will not break if dropped from a 4 foot height.
4. The slides can be sent by U.S. Mail or any courier service to the CL/B (see shipping instructions in the MOP Chapter 8).
5. Special temperatures or handling requirements are not necessary.
6. A second sample collection kit labeled **"Core Biopsy Kit"** contains a slide box with a barcode so those samples can be entered into GlobalTrace once ready to send

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Shipping Procedures: FedEx Overpak

- FedEx shipping bags are pre-labeled with UN3373 and Class B labels according to IATA PI650.
- After samples are scanned and packaged for shipment, complete the FedEx label and attach to the mailing pouch as indicated.
- FedEx UN3373 shipping bags will be included with the project supplies
- All shipments are made at ambient temperature!!

Notify FedEx for sample pick-up or personally deliver package to a FedEx location.



Do NOT place package in a FedEx drop box!

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Category B – Shipping

Peripheral Blood & Bone Marrow kits

Eyebrow hair kit

Buccal swab kit

ALL Specimens from SAME participant may be shipped together as long as they are contained in appropriate kits

Include GlobalTrace manifest

Slide kit

Contact FedEx for pick up for delivery by 8 am next day (FedEx First Overnight);
If samples are collected on Friday, please select Saturday delivery!

Samples cannot be left at drop box!!!!

Trouble-Shooting

1. Contact the CL/B with question or concern that arises during the sample acquisition and shipping procedures
2. Contact the CL/B if there is a broken tube or damage to the kit.
3. If a participant is present at the site and a collection tube breaks or is unusable, it can be replaced with one from the site if available.
4. If the appropriate replacement tube is not available, a tube from another MDS biospecimen collection kit can be used. Scan the replacement kit ID into GlobalTrace to populate the tubes. Include all unused tubes from the replacement kit with shipment and indicate zero volume in GlobalTrace.
5. Check each kit and tube listed in GlobalTrace carefully before shipping to the CL/B. Primary tracking occurs at the "kit" level. The original packaging should be returned exactly as delivered from the CL/B.
6. If the tubes do not match the "kit ID", then the shipment will be rejected in GT and every effort will be made to correct the inconsistency.

Trouble-Shooting

Absorbent material for MDS Kit

Absorbent sleeve

Additional packing material should be added if tubes are loose. Acceptable absorbent material is shown below:

- Cellulose wadding
- Cotton balls
- Super-absorbent packets
- Paper towels

Trouble-Shooting

If extra FedEx UN 3373 overpaks are unavailable, then shipping boxes with appropriate IATA labeling may be used as an alternative.

Fedex Overpak 3373 or box

Box

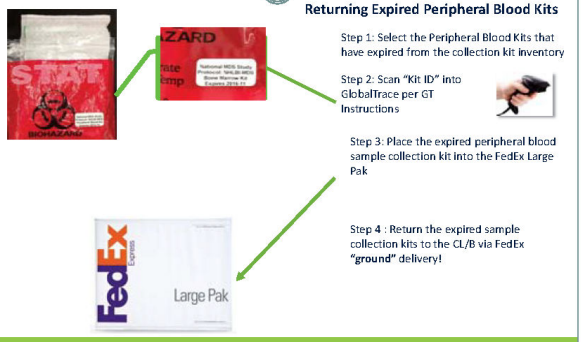
Returning Expired Kits

1. Expiration dates are located on the outside of each "kit" and on the tubes sent from the CL/B
2. When returning an expired kit, the "kit" ID barcode should be scanned into GlobalTrace to populate the collection kit within the electronic system (See GlobalTrace training for additional details)
3. Return ONLY the **expired kit** and not the entire shipment
4. The "kit" should be returned in its ***original*** packaging
4. Ship expired kits to the CL/B in a FedEx Large Pak via **"ground"** delivery!

Shipping Materials

1. The CL/B will provide replacement specimen collection kits and shipping supplies **prior to** the expiration date
2. If a sample collection kit has expired and you have not received a replacement kit, please notify the CL/B immediately
3. Biospecimen collection, returning expired collection kits, bar code scanning and sample shipping are all critical elements for the success of this project!

Returning Expired Peripheral Blood Kits

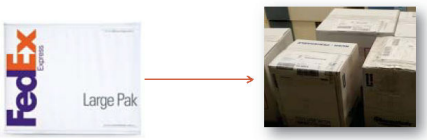


Returning Expired Bone Marrow Kits



Trouble-Shooting

1. Contact the CL/B with question related to the return of expired sample collection kits.
2. Check each kit listed in GlobalTrace carefully before shipping to the CL/B. Primary tracking occurs at the "kit" level. The original packaging should be returned exactly as delivered from the CL/B.
3. If the tubes do not match the "kit ID", then the shipment will be rejected in GT and every effort will be made to correct the inconsistency.
4. If FedEx Large Paks are unavailable, then shipping boxes may be used as an alternative.



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Shipping Procedures: Expired Sample Collection Kits

- After expired sample collection kits are scanned and packaged for shipment, attach the provided FedEx label
- FedEx Large Pak shipping bags will be included with the project supplies
- Expired sample collection kit returns are sent via FedEx **"ground"** delivery
- Ship expired sample collection kits to:

  M2Gen
  10902 N. McKinley Drive
  Tampa, FL 33612
  ATTN: Jeff Painter
  Ph: 813-745-6726

Notify FedEx for package pick-up or personally deliver to a FedEx location.



Do NOT place package in a FedEx drop box!

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Shipping Quality Control

1. Ensure that biospecimen collection times and shipping times are documented for quality control monitoring.
2. Ensure all biospecimens are packaged / wrapped to keep from being damaged during package handling. Be sure each individual biohazard bag is sealed.
3. Remember to include a copy of the GlobalTrace manifest with the study biospecimens.

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Shipping Quality Control *(continued)*

Ship all biologic samples via FedEx "First Overnight"

Notify FedEx for package pick-up or personally deliver package to a FedEx location.

If samples are collected on Friday, select Saturday delivery!

DO NOT PLACE SAMPLES IN A FEDEX DROP BOX!!

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Quality Metrics

1. Site performance will be enrollment driven by comparing expected versus actual accruals, time from sample collection to sample delivery at the CL/B, and volume and completeness of biospecimen collection. Details are provided in Section 8 of the MOP
2. Performance concerns will be addressed through follow-up conference calls with appropriate site personnel to discuss chronic errors and provide guidance as necessary
3. On-site evaluation is possible if required
4. Quality Control will be an ongoing process and the CL/B will work with each site, as needed, to identify and remedy problems

Courier Information

1. Ensure the shipping label is correct.
2. The FedEx account information will be provided after training is complete and the site is approved for participant enrollment.
3. Print the FedEx label and use the MDS Study designated FedEx account number.

Shipping Address

1. Sample processing and storage will take place at the Central Laboratory and Biorepository (CL/B)
2. The CL/B is located at M2Gen Corporation, which is associated with the Moffitt Cancer Center & Research Institute in Tampa, FL.
3. All samples collected for this protocol will be shipped to:

MDS Central Laboratory & Biorepository
M2Gen
10902 N. McKinley Drive
Tampa, FL 33612
ATTN: Jeff Painter
Ph: 813-745-6726



NOTE: Do Not Ship Samples to Moffitt Cancer Center

Contacts at the CL/B

The Central Laboratory and Biorepository (CL/B) will assist in identifying any challenges a clinical team may have in operationalizing the protocol and performing the required sample collection procedures.

For questions or assistance please contact:

Mary Ellen Walker, RN, MSN
CL/B Clinical Coordinator at 813-384-5033
Mary.Walker@m2gen.com

OR

Jeffrey S. Painter, BS
CL/B Biorepository Specialist at 813-384-6726
Jeff.Painter@Moffitt.org

Links and Contact Information

Optional Training Materials:

1. IATA Training:
   - http://www.iata.org/training/courses/Pages/index.aspx
   - http://www.fedex.com/us/services/pdf/HazmatShippingGuide.pdf
2. Study Website:
   - https://thenationalmdsstudy.net/
3. MDS Classification: International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3):
   - http://www.who.int/classifications/icd/adaptations/oncology/en/

CL/B PI:
PK Epling-Burnette, PharmD, PhD
Moffitt Cancer Center
Email: Pearlie.Burnette@moffitt.org
Phone: 813-745-6177

Study Chair:
Mikkael Sekeres, MD, MS
Cleveland Clinic Taussig Cancer Institute
Phone: (216) 445-9353

Study Chair Liaison:
Brianna Johnson
The Emmes Corporation
Email: bjohnson@emmes.com
Phone: (301)251-1161 x17459

The National Myelodysplastic Syndromes Natural History Study
Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

This Concludes Your Training Module for Biospecimen Shipping

THANK YOU!

Presented by the:
Central Laboratory and Biorepository (CL/B)
Moffitt Cancer Center/M2Gen, Tampa, FL

17.0 APPENDIX III SITE INFORMATION CHECKLIST

The National MDS Study: Site Information Checklist

NCI Site Code(s): _____

NCI Site Name(s):_____

Clinical Research Staff

Clinical Research Staff involved in sample collection and shipping associated with the National MDS Protocol (RNs, coordinators, data managers, ARNPs, PAs, etc). At least one IATA certified staff member must be identified.

Name: _____ Title:_____
Role:_____
Address:_____ City:_____ State: ___ Zip Code:_____
Phone:_____ Fax:_____ E-mail:_____
IATA Certification ☐ Yes ☐ No If yes, type of certification_____ Date of certification_____

Name: _____ Title:_____
Role:_____
Address:_____ City:_____ State: ___ Zip Code:_____
Phone:_____ Fax:_____ E-mail:_____
IATA Certification ☐ Yes ☐ No If yes, type of certification_____ Date of certification_____

Name: _____ Title:_____
Role:_____
Address:_____ City:_____ State: ___ Zip Code:_____
Phone:_____ Fax:_____ E-mail:_____
IATA Certification ☐ Yes ☐ No If yes, type of certification_____ Date of certification_____

NOTE: Please attach the IATA Certification for any certified staff members who will be shipping research samples.

Pathology and Laboratory

Primary Pathologist for the protocol (please provide if available)

Name: _____
Address:_____ City:_____ State: ___ Zip Code:_____
Phone:_____ Fax:_____ E-mail:_____
Board Certification:☐ yes ☐ no Specialty/Subspecialty:_____
NCI Investigator Registration Number:_____
Hospital Affiliation(s):_____

Additional Pathologists that may be assisting (please provide if available)

Name: _____
Address:_____ City:_____ State: ___ Zip Code:_____
Phone:_____ Fax:_____ E-mail:_____
Board Certification:☐ yes ☐ no Specialty/Subspecialty:_____
NCI Investigator Registration Number:_____
Hospital Affiliation(s):_____

Name: _____
Address:_____ City:_____ State: ___ Zip Code:_____
Phone:_____ Fax:_____ E-mail:_____
Board Certification:☐ yes ☐ no Specialty/Subspecialty:_____
NCI Investigator Registration Number:_____
Hospital Affiliation(s):_____

Name: _____
Address:_____ City:_____ State: ___ Zip Code:_____
Phone:_____ Fax:_____ E-mail:_____
Board Certification:☐ yes ☐ no Specialty/Subspecialty:_____
NCI Investigator Registration Number:_____
Hospital Affiliation(s):_____

Facility preparing the **cytogenetic reports**:
Facility:_____
Address:_____ City:_____ State:___ Zip Code:_____
Phone:_____ Fax:_____

Clinic and Laboratory Facilities

1. Does your facility have a designated "MDS Clinic" day? ☐ Yes ☐ No
   If yes, please provide the day. If no, how and where will participants be identified?
   _____

2. How many **newly diagnosed MDS subjects** does your facility see in a 6 month period that could participate? _____

3. When do you expect to begin enrolling subjects into the **National MDS Protocol?** (Please provide month/year) _____

4. Is there adequate storage space for study supplies at your site? ☐ Yes ☐ No

5. Is there a laboratory (or lab area) "on site" for processing and packaging research specimens? ☐ Yes ☐ No
   If no, what is the name and location of the laboratory used for clinical research?
   _____

6. Where at your site (clinic, lab, etc.) will the samples for germline DNA be collected (eyebrow hair and buccal swab)?

   _____

7. Where at your site will the bone marrow aspiration and/or biopsy be performed?

   _____

8. Where at your site will the peripheral blood collection be performed?

   _____

9. Does your site have 1D barcode scanners available in the locations listed above? Sites must scan or manually enter specimen collection kit identification numbers into GlobalTrace for specimen tracking. ☐ Yes ☐ No

10. If the peripheral blood collection and bone marrow aspiration are performed at different locations, what is your site's plan to coordinate collection and shipment of samples to the CL/B from various locations within the requested time frame?

    _____

11. Is there a staff member identified to coordinate collection and shipment of samples?
    ☐ Yes ☐ No
    If yes, please provide their name: _____

12. Are peripheral blood and bone marrow slides prepared bedside or in a pathology lab? How will your site ensure the slides are shipped to the CL/B? Please describe below.

    _____

13. Will the pathology slides be reviewed by a pathologist prior to shipment to the CL/B?
    ☐ Yes ☐ No

Additional Notes

_____

_____

Information Provided By: _____

Name: _____ **Title:** _____ **Phone:** _____

Please submit the completed checklist to the CTSU Regulatory Office via the Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

Checklist Approved By (CL/B Reviewer): **Date:**

18.0 APPENDIX IV PARTICIPANT-COMPLETED QUESTIONNAIRES

The QUALMS © 2013 Dana-Farber Cancer Institute, Boston, MA

The Quality of Life in Myelodysplasia Scale

Patients often have different experiences over the course of their illness; however, please limit your responses to your experience **over the past week only**. The information you provide will remain strictly confidential.

	During the past week, how often…	Never	Rarely	Sometimes	Often	Always
1	…did you feel as though there was a lack of clear information about your disease?	☐	☐	☐	☐	☐
2	…have you felt there was limited emotional support available for patients with MDS beyond their families?	☐	☐	☐	☐	☐
3	…did you feel as though you couldn't do anything about your disease?	☐	☐	☐	☐	☐
4	…did you feel the course of your disease was unpredictable?	☐	☐	☐	☐	☐
5	…did you have difficulty explaining MDS to your friends or family?	☐	☐	☐	☐	☐
6	…did you have trouble concentrating?	☐	☐	☐	☐	☐
7	…have you considered changing long-term plans due to health concerns?	☐	☐	☐	☐	☐
8	…have you experienced shortness of breath?	☐	☐	☐	☐	☐
9	…did low energy levels cause you to change your schedule?	☐	☐	☐	☐	☐
10	…did you feel as though your life was organized around medical appointments?	☐	☐	☐	☐	☐
11	…have you felt a sense of hopelessness?	☐	☐	☐	☐	☐
12	…have you been worried about getting an infection?	☐	☐	☐	☐	☐
13	…have you had sufficient energy for routine tasks?	☐	☐	☐	☐	☐
14	…were you afraid of dying?	☐	☐	☐	☐	☐
15	…did you feel angry about your diagnosis?	☐	☐	☐	☐	☐
16	…were you worried about bleeding?	☐	☐	☐	☐	☐
17	…did you feel a sense of gratitude for a part of life that you took for granted before?	☐	☐	☐	☐	☐
18	…did you feel nauseated?	☐	☐	☐	☐	☐
19	…did you worry about your MDS progressing or developing into leukemia?	☐	☐	☐	☐	☐
20	…did you take into account that you might be fatigued when planning your activities?	☐	☐	☐	☐	☐

Version 3.November 2014

Please continue on to the next page →

For the following questions, please again mark the answer choice that best represents your experiences and feelings **over the past week**. The information you provide will remain strictly confidential.

	During the past week, how often…	Never	Rarely	Sometimes	Often	Always
21	…were you concerned that your MDS caused a financial burden for you or your family?	☐	☐	☐	☐	☐
22	…did you feel your family relationships were strained by your disease?	☐	☐	☐	☐	☐
23	…have you felt weak?	☐	☐	☐	☐	☐
24	…have you been too tired to take on the responsibilities you used to have?	☐	☐	☐	☐	☐
25	…did you worry about becoming a burden to your friends or family?	☐	☐	☐	☐	☐
26	…were you unable to participate in activities you are used to doing?	☐	☐	☐	☐	☐
27	…have you felt anxious about test or lab results?	☐	☐	☐	☐	☐
28	…did you avoid crowds because of fear of getting an infection?	☐	☐	☐	☐	☐
29	…did you find yourself grateful for tomorrow?	☐	☐	☐	☐	☐
30	…did you feel you were able to find quality information about MDS treatments?	☐	☐	☐	☐	☐
31	…were you concerned about bruising?	☐	☐	☐	☐	☐
32	…did you feel as though there were a lack of concrete answers about what will happen with your MDS?	☐	☐	☐	☐	☐
33	…did you experience a change in bowel habits?	☐	☐	☐	☐	☐

For the following questions, **you may select "not applicable"** if the question does not apply to you.

	During the past week, how often…	Never	Rarely	Sometimes	Often	Always
34	…were you afraid of losing your job? (**check here** ☐ if not applicable because you are unemployed/retired)	☐	☐	☐	☐	☐
35	…did you feel too tired to drive? (**check here** ☐ if not applicable because you do not drive)	☐	☐	☐	☐	☐
36	…were you afraid to have sex due to your blood counts? (**check here** ☐ if not applicable because you are not currently sexually active)	☐	☐	☐	☐	☐
37	…were you afraid that your MDS treatment would stop working? (**check here** ☐ if not applicable because you are not currently being treated)	☐	☐	☐	☐	☐
38	…have you been too tired to take care of a family member or loved one? (**check here** ☐ if not applicable because you are not providing such care)	☐	☐	☐	☐	☐

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Thank you for completing the QUALMS.

PROMIS Item Bank v. 1.0 - Fatigue -Short Form 7a

Fatigue - Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

English (Universal)
Copyright 1987, 1997



Health Questionnaire

English version for the UK

Sample

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Sample

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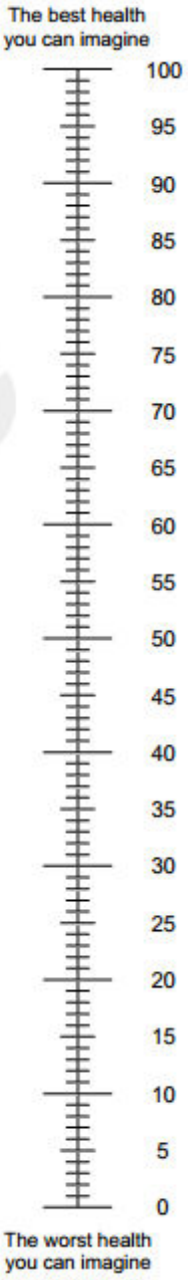
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Sample

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VES-13

1. Age _____

SCORE: *1 POINT FOR AGE 75-84*
3 POINTS FOR AGE ≥ 85

2. In general, compared to other people your age, would you say that your health is:

- ☐ Poor,* *(1 POINT)*
- ☐ Fair,* *(1 POINT)*
- ☐ Good,
- ☐ Very good, or
- ☐ Excellent

SCORE: *1 POINT FOR FAIR or POOR*

3. How much difficulty, on average, do you have with the following physical activities:

	No Difficulty	A little Difficulty	Some Difficulty	A Lot of Difficulty	Unable to do
a. stooping, crouching or kneeling?	☐	☐	☐	☐ *	☐ *
b. lifting, or carrying objects as heavy as 10 pounds?	☐	☐	☐	☐ *	☐ *
c. reaching or extending arms above shoulder level?	☐	☐	☐	☐ *	☐ *
d. writing, or handling and grasping small objects?	☐	☐	☐	☐ *	☐ *
e. walking a quarter of a mile?	☐	☐	☐	☐ *	☐ *
f. heavy housework such as scrubbing floors or washing windows?	☐	☐	☐	☐ *	☐ *

SCORE: *1 POINT FOR EACH * RESPONSE IN Q3a THROUGH f . MAXIMUM OF 2 POINTS.*

4. Because of your health or a physical condition, do you have any difficulty:

a. shopping for personal items (like toilet items or medicines)?

- ☐ YES → Do you get help with shopping? ☐ YES * ☐ NO
- ☐ NO
- ☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

b. managing money (like keeping track of expenses or paying bills)?

- ☐ YES → Do you get help with managing money? ☐ YES * ☐ NO
- ☐ NO
- ☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

Continued

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c. walking across the room? USE OF CANE OR WALKER IS OK.

☐ YES → Do you get help with walking? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

d. doing light housework (like washing dishes, straightening up, or light cleaning)?

☐ YES → Do you get help with light housework? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

e. bathing or showering?

☐ YES → Do you get help with bathing or showering? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

SCORE: *4 POINTS FOR ONE OR MORE * RESPONSES IN Q4a THROUGH Q4e*

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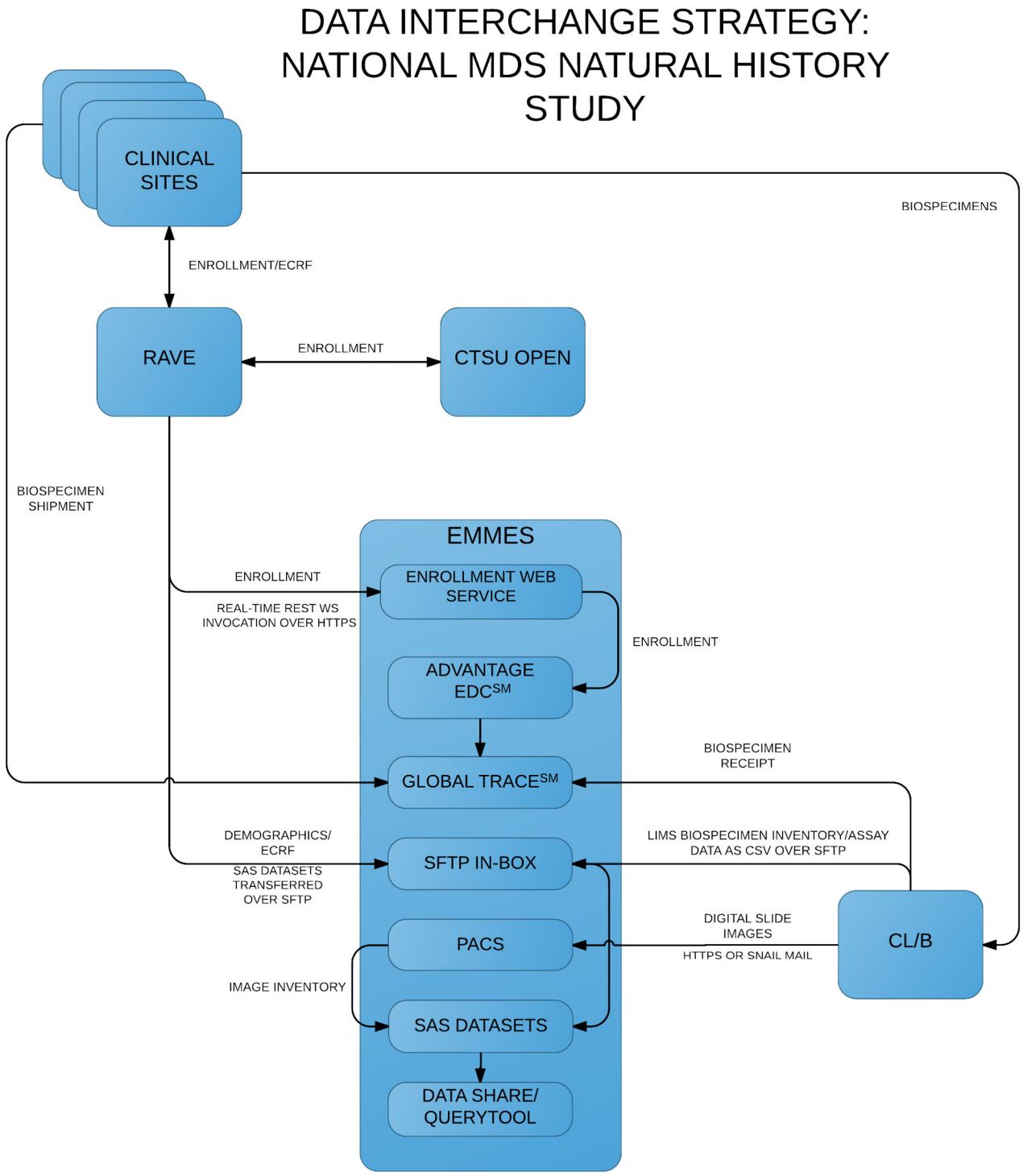
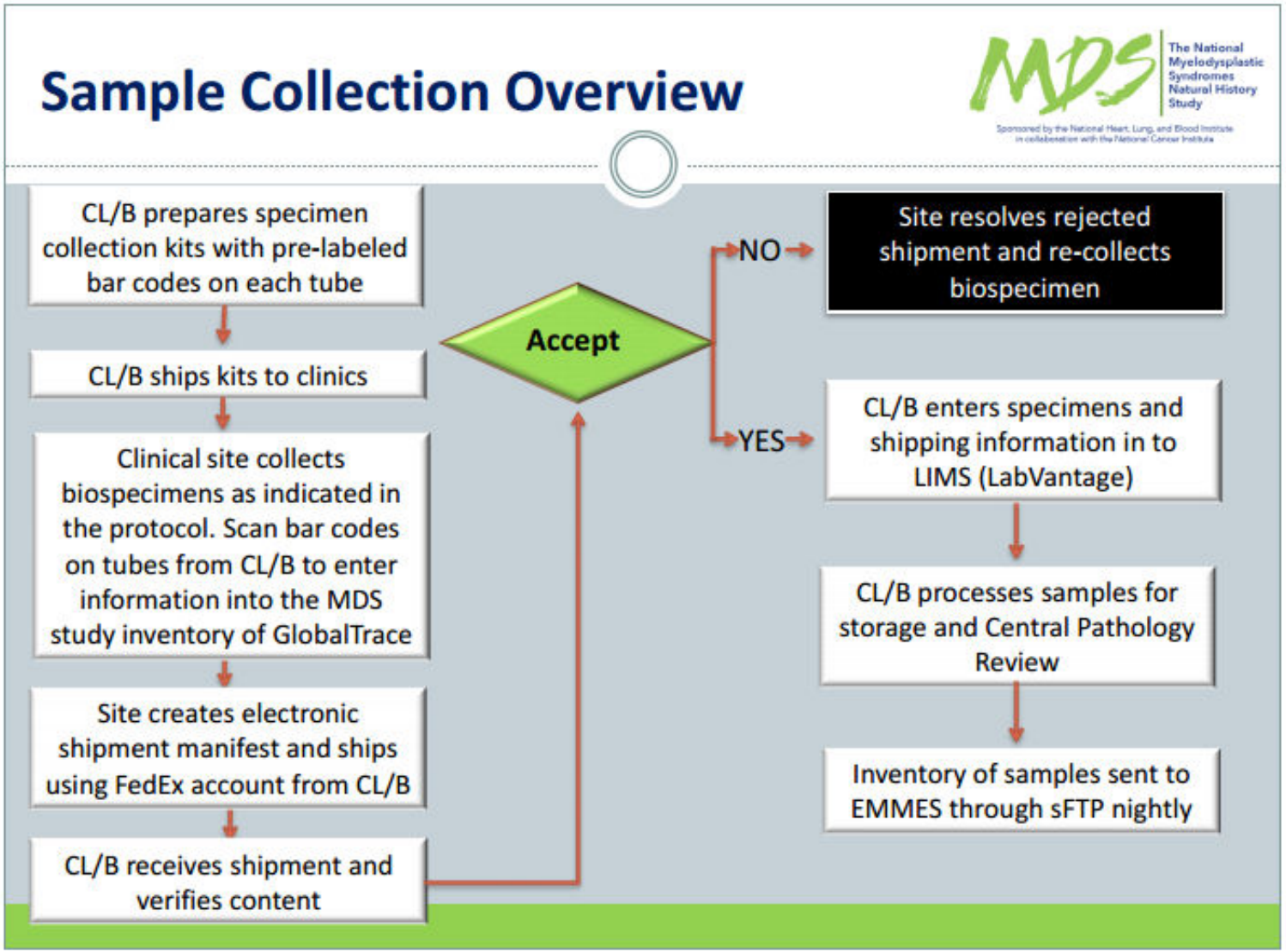
19.0 APPENDIX V DATA INTERCHANGE STRATEGY



20.0 APPENDIX VI SAMPLE COLLECTION OVERVIEW



21.0 APPENDIX VII CONTACT INFORMATION

Group	Contact Information	Reasons for Contact
CL/B	National MDS Study Clinical Coordinator Mary Ellen Walker, RN, MSN Phone: (813) 745-5033 Email: mds_clb@moffitt.org Biorepository Specialist Jeff Painter Phone: (813) 745-6726 Email: mds_clb@moffitt.org	• Specimen Collection Questions • Pathology Questions • Shipping Questions • Rejected Shipments in GlobalTrace • Requesting Barcode Scanner for Study Use
CTEP	Investigator Registration Help Desk Email: pmbregpend@ctep.nci.nih.gov Associate Registration Help Desk Email: ctepreghelp@ctep.nci.nih.gov	• CTEP-IAM Account • Investigator Registration • Associate Registration
CTSU	CTSU Help Desk Phone: 1-888-823-5923 Email: ctsucontact@westat.com Website: https://www.ctsu.org To Submit Site Registration Documents: CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866-651-2878 FAX: (215) 569-0206 Email: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)	• Site Registration • OPEN Questions
DCC	The Emmes Company Email: mdscontact@emmes.com Phone: (301) 251-1161	• Protocol Questions • MOP Questions • eClinical/GlobalTrace General Questions • MDS Website
ECOG-ACRIN	Conor Beath, Data Associate Email: cbeath@ecog-acrin.org Phone: 857-504-2900 Henry Baptista, Project Leader Email: hbaptista@ecog-acrin.org Phone: 857-504-2900	• Medidata Rave Questions • Data Queries in Medidata Rave