NHLBI-MDS

The National Myelodysplastic Syndromes (MDS) Study

Sponsored by the National Heart, Lung, and Blood Institute

In collaboration with The National Cancer Institute

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CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
Rev. 1/17 **For clinical questions (i.e., patient eligibility or treatment-related)** Contact the Study Chair Liaison.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	aplastic anemia
AML	acute myeloid leukemia
ANA	antinuclear antibody
BM	bone marrow
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BSC	best supportive care
CBC	complete blood count
CDUS	Clinical Data Update System
CHIP	clonal hematopoiesis of indeterminate potential
CI	confidence interval
CIBMTR	*Center for International Blood and Marrow Transplant Research*
CIRB	*Central Institutional Review Board*
CITN	*Cancer Immunotherapy Trials Network*
CL/B	Central Laboratory / Biorepository
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
Rev. Add7 COVID-19	Novel Coronavirus Disease 2019
CRA	Clinical Research Associate
CPC	Cancer Prevention and Control
CTEP	Cancer Therapy and Evaluation Program
CTEP-IAM	Cancer Therapy and Evaluation Program – Identity and Access Management
CTSU	Cancer Trials Support Unit
CV	curriculum vitae
DNA	deoxyribonucleic acid
ECOG-ACRIN	Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network
EDTA	ethylenediaminetetraacetic acid
EPO	erythropoietin
EQ-5D-5L	Euro QOL – 5 Dimensions – 5 Levels
FAB	French American British
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
FISH	fluorescence in situ hybridization
FLAER	fluorochrome-conjugated version of a non-lysing, mutated form of proaerolysin
GINA	Genetic Information Nondiscrimination Act
GWAS	Genome-wide Association Study
HCT	hematopoietic cell transplantation
H&E	hematoxylin and eosin
HHS OMB	U.S. Department of Health & Human Services – Office of Management and Budget
HIPAA	Health Insurance Portability and Accountability Act
HMA	hypomethylating agents
IATA	International Air Transport Association
ICU	Intensive Care Unit
ICUS	idiopathic cytopenia of undetermined significance

IDF	Investigator Data Form
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
FACT-G	Functional Assessment of Cancer Therapy - General
LDH	lactate dehydrogenase
LGL	large granular lymphocytic leukemia
LPO	last patient out
MAF	minor allele frequency
MDS	myelodysplastic syndromes
MOP	Manual of Procedures
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
OPEN	Oncology Patient Enrollment Network
OSMB	Observational Study Monitoring Board
PCV	polycythemia vera
PI	Principal Investigator
PNH	paroxysmal nocturnal hemoglobinuria
PROMIS	Patient Reported Outcome Measurement Information System
QUALMS	Quality of Life in Myelodysplasia Scale
QOL	Quality of Life
RA	refractory anemia
RAEB	refractory anemia with excess blasts
RARS	refractory anemia with ring sideroblasts
RNA	ribonucleic acid
RSS	Regulatory Support System
SEER	Surveillance, Epidemiology, and End Results
SNP	single nucleotide polymorphic allele
SOP	Standard Operating Procedure
TCR	T cell receptor
TIBC	total iron binding capacity
TSH	thyroid-stimulating hormone
VES	Vulnerable Elders Survey
W/G	Wright-Giemsa
WHO	World Health Organization

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THE NATIONAL MDS STUDY

A Prospective, Multi-Center Cohort Supporting Research Studies in MDS Natural History

Rev. Add7 Study Chairpersons: Mikkael Sekeres MD MS, Amy DeZern MD (Deputy Chair)

Objectives: The goal of the National MDS Study is to establish a publicly available resource to facilitate the study of MDS natural history. This will be accomplished through: 1) Creation of a multi-institutional, longitudinal biorepository of consistently processed and clinically well-annotated blood and tissue specimens collected prospectively from participants with MDS and participants with idiopathic cytopenia of undetermined significance (ICUS); and 2) Support for investigator-initiated studies of MDS that will have high-impact for MDS patients, including basic science, clinical, health outcomes and epidemiological research.

Study Design: Multi-center, prospective cohort study enrolling patients from centers in the National Cancer Institute (NCI) National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP).

Rev. Add8 Accrual Objective: Approximately 2000 cases of suspected or newly diagnosed MDS or MDS/MPN overlap disorders.

Accrual Period: Approximately seven years

Eligibility Criteria:

a. 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**

b. Diagnosed with de novo or therapy-related MDS within 12-months of enrollment per the World Health Organization (WHO) criteria[1] and undergoing clinical evaluation and planned bone marrow assessments to confirm MDS or to evaluate disease status

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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

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

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

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

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

[1] See Appendix IIIAppendix II for WHO peripheral blood and bone marrow findings in MDS.

Expected Duration of Participation: Participants may be followed for life. Biological specimens will be collected, processed, and stored at the study's Central Lab and Biorepository (CL/B) (MIOMES/Moffitt Cancer Center). Clinical data will be aggregated from study centers in the NCTN and NCORP networks, and stored at the Data Coordinating Center (The EMMES Corporation). Linkage between clinical data and the biorepository will be maintained. Biospecimens and data collected as part of the Study will be delivered to the NHLBI to be used as a scientific resource by the research community. NHLBI will serve as the custodian of the scientific resource and will distribute materials to qualified investigators with approved research protocols.

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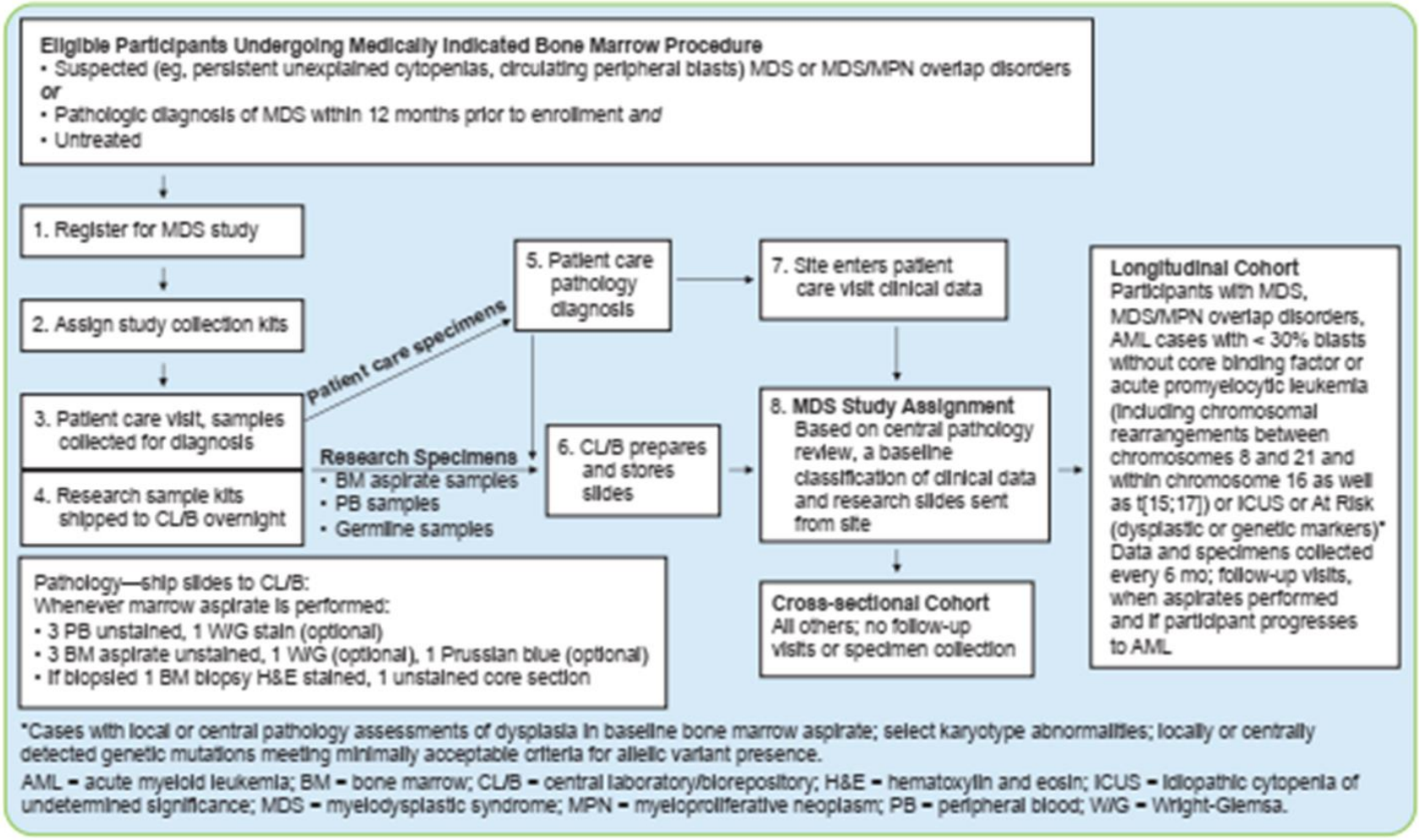
Schema



1. Introduction

1.1 Summary

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 myelodysplastic syndromes (MDS). This will be accomplished by creating a standardized clinical dataset linked to a prospectively collected, consistently processed, and well-characterized biospecimen repository derived from approximately 2000 participants with suspected or newly diagnosed MDS or MDS/myeloproliferative neoplasm (MPN) overlap. The establishment of this national resource will enable scientists to address research questions in MDS that have been impractical to study through single or multi-institutional cooperative efforts, through retrospective studies, or through other disease registries. The National MDS Study will facilitate the understanding of MDS pathogenesis and progression; enhance MDS diagnosis, classification, prognosis, and survivorship; inform medical decision making for MDS patients; facilitate biomarker discovery; help identify new therapeutic targets as well as define the optimal use of existing therapies; and inform efforts to understand disease etiology and prevention. This publicly funded resource will be made available to the broader scientific community interested in MDS research. Such efforts will likely include genetics studies. Inclusion of the ICUS group will provide insights to such questions as: Are the number and types of clonally restricted somatic mutations different than MDS patients at entry? Do individuals perceived quality of life differ between the two groups? Is there a difference in care utilization for early MDS and ICUS individuals?

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1.2 Background and Significance

1.2.1 Overview of Myelodysplastic Syndromes

The myelodysplastic syndromes (MDS) are a group of clonal hematopoietic disorders displaying extensive heterogeneity in clinical presentation, prognosis, and molecular pathology.[1-3] Although MDS display features of malignancy, it is not universally agreed that MDS constitute cancer.[4] However, MDS are reported to the NCI Surveillance, Epidemiology and End Results (SEER) program. Estimates from SEER suggest there are 15-20,000 new cases of MDS annually in the US,[5] although medical claims data suggest there may be closer to 30,000 new cases per year in the US.[6,7] This would place the incidence of MDS in men on par with that of leukemia (30,100 new cases expected in the US in 2014) and the incidence of melanoma of the skin in women (32,210 new cases expected in the US in 2014), which are the 9th and 7th most common cancers in men and women, respectively.[8]

MDS are diagnosed primarily in older adults, with men diagnosed more frequently than women, and with an incidence that increases progressively with age.[9] MDS occur *de novo* (~90% of MDS) as well as secondary to cancer treatment with ionizing radiation, chemotherapy, or other bone marrow failure conditions, and through environmental causes (~10% of MDS).[10-12] Disease severity varies

widely at diagnosis, although most cases have a tendency to exacerbate over time.[2] Previously considered a "pre-leukemic" syndrome, it is now understood that only about 30% of all MDS transform to acute myeloid leukemia (AML), the likelihood of transformation being significantly higher with increasing disease severity.[2,13] In addition, the presence of rare variants such as the "overlapping" disorders that display features of both myelodysplasia and MPN, and the existence of hypoplastic (as opposed to the typical hypercellular) MDS pose difficulties in researching etiology and pathogenesis and developing appropriate therapies.[14,15] The heterogeneity in MDS suggests the various subtypes may not represent a single disease entity. MDS constitute a spectrum of different progressive diseases with potentially different etiologies, some of which terminate in frank leukemia, while other, pathologically distinct variants may lead to progressive marrow failure.[2,16,17] Related disorders such as ICUS and the recently reported clonal hematopoiesis of indeterminate potential (CHIP) present complex clinical conditions, the understanding of which could benefit from parallel studies of MDS.[18]

Treatments for MDS depend upon disease severity at diagnosis, and range from supportive care to hypomethylating agents (HMA), cytotoxic chemotherapy, and hematopoietic cell transplantation (HCT).[19] HCT is the only available therapy with curative potential, although it is associated with substantial morbidity and risk of fatal complications, and may not be an appropriate therapy for all patients.[20] It is only considered in < 5% of MDS patients, and thus for approximately 95% of patients, therapeutic approaches are ultimately palliative.[11] Thus, more translational research is required to determine optimum strategies for distinct patient subgroups. The estimated 3-year survival of MDS patients relative to age-matched controls is 42%.[21] As the incidence of MDS increases with age,[9] and people live progressively longer lives, there is an urgency and necessity to better understand the natural history of MDS and identify new preventive and therapeutic interventions. Given the rarity and extensive heterogeneity of MDS, details of natural history can only be studied in the context of multi-center collaborations that facilitate close, protocol-specified longitudinal follow-up of a large patient cohort that is representative of the broad spectrum of the disease.

Therefore, the primary objective of the National MDS Study is to establish a longitudinal cohort of up to 1750 participants recently diagnosed with MDS and MDS/MPN overlap disorders. This cohort will provide a standardized clinical dataset linked to a prospectively collected, consistently processed, and well-characterized biospecimen repository that will facilitate the understanding of MDS etiology, pathogenesis and progression; enhance the accuracy of MDS diagnosis, classification, prognosis and survivorship; inform medical decision making for MDS patients; facilitate biomarker discovery; help identify new therapeutic targets as well as define the optimal use of existing therapies; and inform efforts at disease prevention.

1.2.2 Discovery and Classification of MDS

What would later be labeled MDS was first observed during the 1920s-1940s as abnormalities in the blood of anemic patients refractory to vitamin B12 therapy.[13] In the early 1950s, after observing the development of leukemia in some patients with refractory anemia, the existence of a pre-leukemic syndrome was proposed.[13] However, this designation was felt by some to be misleading as a substantial proportion of patients with characteristics of the pre-leukemic syndrome never developed leukemia and instead survived long periods before dying of other causes.[13] Thus, it was suggested that this condition be referred to as “myelodysplastic diseases” or “myelodysplasia.”[13] Finally, in 1976 and 1982 the French American British (FAB) working group proposed the first classification of MDS, which was based primarily on morphological features.[22,23] This classification included refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), refractory anemia with excess blasts (RAEB) and RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). The original FAB classification has since been supplanted by the World Health Organization (WHO) system[24] (**Table 1, Appendix II**)**.** The most notable changes from the FAB system to the WHO 2008 classification are:

- RAEB-T is no longer considered MDS and has been reclassified as AML
- CMML is not present in the WHO classification because it is now classified as an “overlap” disorder that displays elements of myelodysplastic and myeloprolilferative neoplasms (MDS/MPN)
- The following categories are new in the WHO classification: RCMD, RCUD, del(5q), and MDS-U

Each subtype has its own likelihood of AML transformation. Some subtypes are diagnosed more commonly than others making estimates of their relative frequencies a challenge to determine accurately. The fact that so many subtypes are identifiable, and that the natural history apparently varies, suggests that MDS is, in fact, a group of distinct diseases, which share the essential feature of hematopoietic failure, but may not share a common pathogenic defect or even a common etiology.

The WHO released the revised classification system for myeloid neoplasms and acute leukemia in May 2016[112]. Both the 2008 and 2016 classifications will be collected for the study, and the 2016 revision for peripheral blood and bone marrow findings and cytogenetics of MDS will be used as the basis for classifying study participants (Appendix III).

Table 1: The World Health Organization (WHO) (2008) Classification of Myelodysplastic Syndromes

WHO Classification	Abbreviation	% of MDS Cases	Distinctive Elements of Natural History
Refractory anemia	RA	10-20%	• Rarely transforms to AML
Refractory anemia with ring sideroblasts	RARS	3-10%	
Refractory anemia with excess blasts**	RAEB	40%	• RAEB-1 -- 25% transform to AML • RAEB-2 -- 33% transform to AML
Refractory cytopenia with multilineage dysplasia	RCMD	30%	• 10% transform to AML
Refractory cytopenia with multilineage dysplasia, with ringed sideroblasts	RCMD-RS		
Refractory cytopenia with unilineage dysplasia	RCUD		
MDS associated with isolated del(5q)*	del(5q)		• Rarely transforms to AML • Associated with long survival • Unlike other MDS, occurs more often in women
Myelodysplastic syndrome, unclassifiable.	MDS-U	< 1%	
Refractory neutropenia	RN	< 1%	
Refractory thrombocytopenia (RT).	RT	< 1%	
Childhood myelodysplastic syndrome		< 1%	

* del(5q) = deletion of the short arm of chromosome 5

** Includes RAEB-1 (2-9% blasts) and RAEB-2 (5-19% blasts)

1.2.3 Diagnosis

MDS subtypes, with the possible exception of del(5q), are defined by morphological criteria such as the blast percentage in the peripheral blood and bone marrow, the type and degree of dysplasia in myeloid cells, and the presence of features such as ring sideroblasts.[24] Such evaluations require the trained eye of a hematopathologist experienced with MDS, and thus diagnosis and case classification can be laborious and subjective. In some cases, there is poor inter-observer reliability.[25-27] Molecular markers have been successfully incorporated into the diagnosis of other hematopoietic diseases such as polycythemia vera (PCV), which is identifiable by characteristic mutations in the *JAK2* gene, and chronic myeloid leukemia (CML), which is identified by the *BCR-ABL* chromosomal re-arrangement.[28] Although a great deal of information is being accumulated regarding the genetic basis of MDS, none of this information is as yet incorporated into diagnostic procedures.[17] Perhaps the primary

reason for this is the extensive molecular heterogeneity of MDS relative to diseases like PCV and CML. With more precise classification of MDS into distinct disease entities, it will be possible to incorporate molecular diagnostic markers into routine clinical practice. Such improvements are badly needed as the current diagnostic process requires a laborious procedure of ruling out the presence of behavioral, infectious, or other hematological etiologies for presenting symptoms.[29-31] Finally, the requirement of visual inspection of pathology specimens by multiple readers may delay diagnosis in a clinical setting, and is impractical in the context of multi-center research studies where such review is required for verification of eligibility criteria.[32] Digital pathology technologies have been developed that may expedite or objectify the diagnostic process,[33] but these have not yet been evaluated for MDS diagnosis per the College of American Pathologists guidelines for disease diagnosis.[34] The National MDS Study will provide an ideal platform to pilot the use of these technologies for MDS diagnosis.

1.2.4 Contemporary Perspectives on MDS

MDS exhibit features of cancer including a neoplastic and clonal behavior with genomic (and epigenomic) changes in oncogenes and tumor suppressors, as well as a malignant failure of hematopoiesis.[17] However, some subtypes of MDS such as MDS associated with the del(5q) cytogenetic abnormality, are relatively indolent, and lower-risk MDS typically require no treatment unless associated with significant cytopenias, transfusion requirements, and/or a compromise in quality of life.[19] Nonetheless, the WHO has defined MDS as a neoplasm,[24,28] it is classified under the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3),[35] and MDS are now reported to SEER.[5] This development suggests that the medical community has adopted the view that MDS are indeed cancer, i.e. a malignant disease. Given this controversy, MDS patients themselves often are not informed that their disease is a cancer and thus, they may demonstrate a limited understanding of the disease natural history and its limited potential for cure. In an online survey of 358 MDS patients conducted in 2009, 80% claimed that their physicians described MDS as a “bone marrow failure disorder.”[36] Only 7% were told they had cancer, 6% were told they had leukemia, and 3.6% were told they had a hematologic malignancy.[36] Only 45% knew their IPSS score, and 35% of patients reported not discussing survival or risk of AML transformation with their physicians.[36] Thirty-seven percent (37%) of patients believed that their current therapy would improve their survival, and 36% were unsure of the value of their current therapy in this regard.[36] Alarmingly, 31% of patients receiving supportive care believed that this therapy would improve survival.[36]

The aforementioned survey is not the only such study to demonstrate the lack of patient understanding of MDS and ineffective communication between patient and physician. In another survey of 477 patients and 107 health care professionals (61 physicians and 59 registered nurses, nurse practitioners, physician assistants, or social workers with a Master of Social Work degree), only 10% of patients

viewed MDS as a cancer whereas 46% of non-physician healthcare workers and 59% of physicians called MDS a cancer.[37] When asked whether MDS were curable, 29% of patients, 33% of non-physicians, and 52% of physicians responded that MDS could not be cured.[37] While only 11% of patients in this study received a curative HCT, 25% claimed their therapy cured their disease and 44% of physicians claimed their patients were cured by the therapy they prescribed.[37]

The lack of shared understanding—between physician and patient, and between healthcare providers—of what MDS are and how therapy might affect prognosis may not be surprising given the extreme diversity of MDS. It is unlikely that a harmonized understanding of MDS will be achieved without an improved understanding of the natural history of MDS.

1.2.5 Etiology

Studies of disease etiology are critical for deriving primary and secondary preventive interventions for disease control. Currently there are no recommendations for preventive measures for MDS, largely because clearly modifiable exogenous risk factors have not yet been definitively identified. Environmental and occupational exposures implicated in MDS etiology include ionizing radiation,[12,38-40] benzene,[41] tobacco smoking,[42] and use of hair dye.[43] However, many studies examined special cohorts such as atomic bomb survivors and factory workers with extreme exposure histories,[40,41] and are thus not relevant for the majority of patients. Contemporary exposure to benzene comes largely from gasoline and cigarette smoke rather than factory work, and there is disagreement over whether regular exposure to low levels of benzene through occupations such as automobile repair is associated with an appreciable risk of hematopoietic malignancies in general, and MDS in particular.[44] Smoking is a relatively consistent risk factor for MDS across studies but cannot explain the majority of cases.[45] To date, no infectious etiology of MDS has been identified, and diet does not appear to be related to MDS.[16]

Most etiologic studies of MDS are hampered by limitations linked directly to our poor understanding of MDS natural history. Inconsistencies and weak findings across studies may be related to the different diseases being studied rather than a single entity, as well as uncertainty regarding the precise classification of MDS cases into subtypes.[25-27] Inconsistency of results may also derive from the use of different classification systems, e.g., FAB vs. WHO,[22,24] and diverse latency periods for the various MDS subtypes. For example, therapy-related MDS have a short latency relative to *de novo*, lower risk types. It is a challenge (and perhaps even inappropriate) to combine these subtypes in studies of MDS etiology. Finally, some rare subtypes such as hypoplastic MDS exhibit pathological behavior quite distinct from other MDS cases (behaving more like aplastic anemia), and should probably be studied separately.[15]

Even the study of endogenous risk factors is hampered by a lack of understanding of MDS natural history. For example, while advanced age is a known risk factor for acquired MDS[9], the disease also can

occur in children.[46] However, the phenotype of MDS may be different than in adults. This is in part because pediatric MDS are more likely to result from an inherited bone marrow failure disorder such as Fanconi anemia whereas the vast majority of MDS in patients over age 40 years, with rare exceptions, is thought to be an acquired disease.[46,47] While male gender is often pointed to as a risk factor for MDS[9], the gender effect in MDS is murky as there are subtypes such as del(5q) in which there is actually a female predominance. Finally, germline predisposition to MDS is possible, e.g., through polymorphic forms of xenobiotic metabolizing enzymes that modify MDS risk in the presence of exogenous exposures.[48]

Thus, the National MDS Study is likely to contribute to etiologic research in the future by clarifying the heterogeneity of MDS through further refinement of disease subtypes, characterization of pathological features of MDS that may suggest likely endogenous and exogenous etiologic factors, and by enhancing the classification and diagnosis of the disease.

1.2.6 Prognosis

Various tools are available to determine MDS prognosis, with each system being useful in predicting survival and selecting therapy for different groups of MDS patients. The International Prognostic Scoring System (IPSS)[49] and more recently, the revised IPSS (IPSS-R) are used widely.[2] The IPSS-R was developed using information from 7,012 patients with primary MDS (from 11 countries) who had not received disease-modifying therapy.[2] **Tables 2** and **3** summarize parameters used and risk groups with their respective median survival.

Table 2: Components of the IPSS-R Prognostic Score (Greenberg, et al.[2])

Score Value	Cytogenetics	Bone Marrow Blast (%)	Hemoglobin	Platelets	ANC
0	Very good	< = 2	> = 10	> = 100	>= 0.8
0.5	-	-	-	50 to < 100	< 0.8
1	Good	> 2 to < 5	8 to < 10	< 50	
1.5	-	-	< 8	-	-
2	Intermediate	5 to 10	-	-	-
3	Poor	> 10	-	-	-
4	Very poor	-	-	-	-

A dash (-) indicates the prognostic factor is not applicable

IPSS = International Prognostic Scoring System Revised

ANC = absolute neutrophil count

[a] Cytogenetic scoring system (Very Good, Intermediate, Poor, and Very Poor) is defined by Greenberg, et al.[2]).

Table 3: Risk Strata Based on the IPSS Score (Greenberg, et al.[2])

IPSS-R Score	IPSS-R Risk Category	Median Survival (95% CI) (years)	Median Time to 25% AML Transformation (years)
< = 1.5	Very low	8.8 (7.8-9.9)	NR (14.5-NR)
> 1.5 to 3	Low	5.3 (5.1-5.7)	10.8 (9.2-NR)
> 3 to 4.5	Intermediate	3.0 (2.7-3.3)	3.2 (2.8-4.4)
> 4.5 to 6	High	1.6 (1.5-1.7)	1.4 (1.1-1.7)
> 6	Very High	0.8 (0.7-0.8)	0.73 (0.7-0.9)

IPSS = International Prognostic Scoring System Revised

NR = not reached

The IPSS and IPSS-R are used to select appropriate therapy for MDS patients. However, the very nature of how the IPSS-R was derived limits its clinical utility. Specifically, because the IPSS-R is based on evaluation of untreated patients, it has not been validated as a tool that can be applied when disease progresses, or after patients receive some disease-modifying therapies. While other prognostic scoring systems have been developed to account for disease progression,[50,51] none addresses the prognostic importance of changing parameters with use of disease-modifying therapies such as hypomethylating agents or HCT. In addition, while existing classifications incorporate cytogenetic abnormalities,[2] nearly half of all MDS patients exhibit normal karyotypes,[1] and those patients are known to express molecular abnormalities that have prognostic relevance but which are not yet routinely incorporated in the scoring systems.[52-54] Therefore, no “complete” system is currently available. Additionally, development of the IPSS and IPSS-R excluded secondary MDS, patients with features of myeloproliferative neoplasms, and patients under age 16 years.[2,49] Thus, much work remains to incorporate molecular information, as well as the type and timing of therapy into clinically accurate and useful prognostic systems for MDS patients, and to expand prognostication to other types of MDS.

1.2.7 Altering the Natural History of MDS through Therapeutic Intervention

Guidelines are available from independent groups in Europe[55] and the United States that specify similar algorithms for selection of therapy in MDS patients based on risk stratification at diagnosis. In general, lower-risk patients are not treated until they become transfusion-dependent and/or symptomatic, when they are treated with erythropoiesis stimulating factors,[56] lenalidomide,[57,58] immunosuppressive agents, or HMAs.[59,60] Higher-risk MDS patients may be referred for HCT if a donor is available and if they are deemed to be a good candidate. If the higher-risk patient is not eligible or is not agreeable to transplant, or as the patient is awaiting transplant, then HMA are given. Of the two HMAs, azacitidine has prospectively shown improvement in overall survival relative to supportive care in a Phase III trial.[61,62] Another HMA, decitabine, has also been compared to BSC in two Phase III trials, and demonstrated improved response rates, but no survival benefit.[63,64]

Significant limitations exist with the currently available MDS therapies. Most importantly, HCT is the only therapy that has curative potential, but carries with it substantial risk as evidenced by transplant-related mortality rates of nearly 40% in some settings.[65] This has deterred many physicians from recommending HCT to their older patients, who paradoxically make up the bulk of higher-risk patients.[66] Additionally, until recently, allogeneic HCT for MDS was not covered by Medicare. Thus, fewer than 1,000 MDS patients are transplanted in the US each year.[67] However, access to HCT may be expanded in the future as many transplant centers are now using less toxic reduced intensity conditioning regimens, and the transplant community is recognizing that age alone is only a weak predictor of HCT outcome.[66,68,69] The appropriate use of HCT depends on more than simply donor selection and conditioning regimen.[70] Optimal timing depends on a patient's risk stratification at diagnosis, as shown in two studies that demonstrated IPSS intermediate-2 or high-risk patients benefit from transplantation soon after diagnosis while IPSS low and intermediate-1 risk patients have better survival and quality adjusted life expectancy when transplant is delayed until disease progression is observed.[71,72]

In addition to these open questions in transplant, options are limited for patients who are not an HCT candidate or for whom no donor is available. While higher-risk MDS patients who are not transplanted may receive a modest survival benefit from HMA, the therapy is not curative and all patients lose their response. While hypomethylation is understood to be the primary mechanism of action for HMA, it has been shown that global methylation and methylation of tumor suppressor genes is not consistently associated with response, suggesting other unknown host or disease-related factors contribute.[54,73] Finally, survival benefits associated with HMA have been observed in studies of higher-risk patients only and the benefit of HMA in lower-risk MDS is not as clear.[61,62] HMA as a therapy is also not without potential complications, including risk of life-threatening infections from worsening cytopenias from therapy. Furthermore, the time to see a response can be protracted over 4-6 cycles of therapy.[61]

Further study of MDS molecular pathogenesis is required to gain insight into why current therapies fail and which targets are available for new therapies.[17] Finally, there has been no large study comparing long-term outcomes of patients on HMA vs. HCT, and few studies that examined HMA use outside of clinical trials have identified reasons for discontinuation or refusal of therapy, or documented the patient/physician decision-making process in selection of transplant vs. non-transplant therapies.[74-78] These important clinical and therapeutic questions are best addressed in a large, multi-institutional, longitudinal cohort using structured data collection instruments paired with available high-quality biospecimens.

1.2.8 Genetic Basis of MDS

Early studies identified mutations in known cancer-associated genes in MDS, including *TP53*, *RAS,* and *RUNX1*.[1] However, while such mutations are frequently observed in MDS, the majority of the disease exhibits the wild type of these genes.[1] Whole genome and whole

exome sequencing studies have since revealed a much richer genetic complexity in MDS than was previously identified using candidate gene studies.[17] It is now known that mutations are common in several families of genes in MDS, including epigenetic regulators and mRNA splicing factors.[17] In addition, mutations have been identified in known oncogenes in normal karyotype MDS, and these mutations are associated with overall survival after adjustment for IPSS score.[53] These observations represent an early understanding of the genetic and epigenetic complexity of MDS that has not yet been incorporated into routine clinical use for prognostication, diagnosis, or therapy.[17] Current knowledge of the genetic basis of MDS, combined with evidence suggesting accumulation of mutations in hematopoietic oncogenes is a common feature of aging, implies that serial investigations are necessary to understand the full impact of genomic changes on development of MDS, its prognosis, and opportunity for intervention.[17,79,80] Furthermore, the observed genetic diversity in MDS implies the need for adequate sample sizes for effective study.[1] Thus, a large, longitudinal cohort such as the National MDS Study is required to facilitate the advancement of knowledge concerning the genetic basis of MDS and translation of this knowledge into clinical practice.

1.3 Quality of Life Component

1.3.1 Background and Rationale for Quality of Life (QOL) Study

QOL is defined by the World Health Organization as the "net consequence of life characteristics on a person's perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns".[81,82] The key to measuring QOL is understanding that it is subjective, reflecting present lifestyle, past experience, hopes for the future, dreams, and ambitions. Despite the importance of QOL to patients with MDS,[83] few studies have been performed to specifically assess the impact of treatments and disease progression on this outcome.[84] Indeed, rigorous measurement of QOL for patients with chronic diseases[85] and specifically for those with MDS has been recognized as a research imperative.[86-88] The current proposed large, publicly-funded, longitudinal MDS patient cohort and the companion ICUS cohort present an unparalleled opportunity to understand the QOL patients with MDS experience, both as compared to patients with other neoplasms, as well as healthy older adults. Moreover, serial assessment will allow characterization of how the QOL of patients with MDS is affected by disease progression and treatments, how it in turn many predict survival, and how QOL concerns might be better understood and leveraged to result in truly patient-centered treatment decision-making.

1.3.2 QOL Study Design

After baseline assessment, we will measure patients' self-reported QOL at 6 and 12 months and annually thereafter. These intervals were chosen given prior experience that has revealed MDS-related

QOL to be relatively stable in shorter periods,[92] and also to help minimize participant response burden.

1.3.3 Rationale for Quality of Life Measure Selection

Four measures have been selected, balancing competing interests of response burden and research usefulness. QOL instruments selected for this study include tools that have been validated and/or used before in MDS research and/or are likely to be employed going forward in studies of MDS and similar older populations. These instruments will allow rigorous study of utilities, fatigue, several domains of general cancer-related QOL, and MDS-specific QOL, incorporate the most relevant PROMIS measure (fatigue) for comparison with non-MDS populations, and also contain two of the measures in the Connect MDS/AML Disease Registry (which may allow for combined analyses with that cohort). These choices also minimize—but do not eliminate—patient response burden (77 questions in the full panel, 12 in the reduced panel used by ICUS cases post baseline).

1. **QUALMS[93]** (38 items). This is a new MDS-specific measure of QOL developed with patient and provider input that has shown promise in an international validation effort (N=266).[94] In that study, the measure was internally consistent (α=.91), and moderately correlated with the EORTC QLQ-C30[95] global scale and its subscales. Patients with Hg < 8 scored lower than those with Hg > 10 (61.8 v 71.3, $p < 0.001$), as did the transfusion-dependent (62.4 v 69.7; $p < .01$). There was good test-retest reliability (r=.76), and significant changes seen for patients hospitalized or with infections between administrations (both p's < 0.01). Factor analysis revealed physical burden, benefit-finding and emotional burden subscales, and the physical burden (QUALMS-P) subscale had even stronger known groups validity.
2. **FACT-G (Version 4)[96]** (27 items). Along with the EORTC QLQ-C30, this measure has been used in many prior studies of cancer, and some studies of MDS.[97-101] This measure is also included in the Connect MDS/AML Disease Registry (as part of the Fact-An).
3. **PROMIS Fatigue Short Form 7a[102]** (7 items). While the short form has not been specifically validated for use in MDS, it has been successfully used in other chronic disease such as multiple sclerosis,[103] and several other short forms (4a, 6b, 10a, and 16), have been used to measure physical functioning in other cancer patients.[104]
4. **EQ-5D-5L[105]** (5 items). The instrument is a simple descriptive questionnaire with a single index value (thermometer) for health status that can be used to develop health utilities for use in health services studies such as decision analyses (as has been done successfully for myeloma).[106] It is also a general measure of QOL. The 5-level (versus 3-level) version reduces ceiling effects and improves sensitivity. This measure is also included in the Connect MDS/AML Disease Registry.

1.4 Rationale

Given the aforementioned summary of the state of knowledge in MDS, we describe below the rationale for the present study in terms of the following unmet needs in MDS research that require the resources of a large, publicly funded, longitudinal MDS patient cohort.

1. There is currently no large, high-quality biospecimen repository available to the broader scientific community interested in MDS research.
    - 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 in important strata, including across clonal populations within the same participant, across disease subtypes, and across risk categories; and this description must be longitudinal in nature in order to address questions relevant to the timing of therapeutic and preventive intervention.
    - 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 cytopenias but not MDS may allow delineation of molecular or other factors uniquely associated with MDS-related cytopenias.

There is currently no publicly available resource that meets these requirements. The National MDS Study will address this unmet need through a multi-center initiative to uniformly collect, process, and store high quality biological specimens and clinical data from a large, prospective cohort of adult 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.

2. The classification of MDS requires additional specificity.
    - Revision of MDS classification from the FAB to WHO systems resulted in the reclassification of some MDS subtypes to AML and expanded the list of known disease subtypes. This is evidence that our understanding of disease heterogeneity continues to grow.
    - The varied morphological, clinical, and genetic features of MDS suggest that it may not be a single disease entity and that the current classification system of MDS requires refinement.
    - Errors in classification of MDS are likely having a negative impact on other areas of research. This is especially apparent in etiologic research where no strong risk factors have been identified that explain the majority of MDS. As of yet there is no primary or secondary prevention available for MDS. In addition, the interaction of host genotype with environmental exposures may influence risk and/or progression of individual subtypes of MDS. However, the presence of low-penetrance disease-modifying

germline polymorphisms with relevance to predisposition to specific subtypes of MDS will require a large cohort to effectively study.

3. Current prognostic systems for MDS are incomplete.
    - Existing prognostic systems incorporate cytogenetic abnormalities, yet nearly half of all MDS patients exhibit a normal karyotype
    - Several studies have indicated the presence of molecular abnormalities even in normal karyotype MDS, and some of this information has prognostic value after controlling for IPSS score
    - MDS is a progressive disease and although some prognostic systems account for disease progression, none include molecular prognostic information
    - Thus, it is known that current prognostic systems for MDS are incomplete, and a well-characterized longitudinal specimen archive will be required to enhance existing prognostic systems with molecular data. Such an effort will not be possible across institutions with varied specimen collection, handling, and assay procedures.
4. The current array of therapies for MDS is limited.
    - Only HCT offers a potential for cure, yet the therapy carries unacceptable risk for some patients. Non-transplant alternatives are limited to HMA, which may extend survival yet not all patients benefit (and the reason is as-of-yet unclear), or supportive care, which is not curative; a comparison of long-term outcomes on HMA vs. HCT has not been done though a study of transplant versus non-transplant therapies for high risk MDS is underway in the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).
    - Further study of the genetic and epigenetic basis of MDS is required to gain insight into why current therapies fail and which targets are available for new, more effective therapies
5. There is a lack of information to support patient-oriented medical decision making in MDS.
    - Study of the effectiveness and comparative effectiveness of therapy for MDS has proven difficult through SEER because data on health outcomes must be obtained via linkage with the Medicare claims database, which does not include patients under age 65 and does not contain quality of life measures, which is a crucial outcome measure for MDS. Single institution studies are unable to provide adequate assessment of transplant vs. non-transplant therapies due to small sample sizes or reliance on medical claims data rather than close, protocol-specified follow-up. In addition, both registry-based and single-institution studies that rely on claims data typically have incomplete data for MDS subtypes.
    - There is an apparent lack of shared understanding—between physician and patient, and between healthcare providers—of what MDS are and how therapy might affect prognosis. This misalignment of perception may be due to the extensive heterogeneity of MDS, and it is not clear whether or how it affects decision making regarding selection of transplant or non-transplant therapies.

6. Improvement of diagnostic efficiency is required in the clinic and to support future MDS research.
    - Diagnosis of MDS using currently available methods requires visual inspection of pathology specimens, often by multiple pathologists. This may delay diagnosis in a clinical setting, and it introduces complexity in the context of multi-center research studies where multi-reader review is required for verification of eligibility criteria. Digital pathology technologies are available which may expedite and/or objectify the diagnostic process, but these have not yet been evaluated for MDS diagnosis per the American College of Pathologists guidelines for disease diagnosis. The National MDS Study provides an ideal platform to pilot the use of these technologies for MDS diagnosis.
7. There is an urgent need to discover biomarkers in MDS.
    - With the exception of the del(5q), the serum EPO level, and the circulating blast percentage, there are no biomarkers available to aid in the selection of therapy for MDS patients.
    - There are no biomarkers available that reliably predict response to therapy.

1.5 Study Organization

The National MDS Study is a research project funded and supported by the National Heart, Lung, and Blood Institute (NHLBI) with collaboration and infrastructure support from the National Cancer Institute (NCI). The study will be governed by a Protocol/Steering Committee who will have responsibility for recommending and reviewing processes for data and specimen access consistent with the goals of the study and NHLBI policy. The Protocol Team/Steering Committee members are nominated by NCTN and NCORP programs, and selected and appointed by NHLBI and NCI staff. This committee also includes members of the Data Coordinating Center and the Central Laboratory/Biorepository. The committee will have responsibilities to plan and design the study activities. The study is observational and does not have therapeutic intent. An independent Observational Study Monitoring Board (OSMB) will review interim study progress and recommend to the NHLBI changes to facilitate study performance while respecting participant safety and contributions. The OSMB will be comprised of individuals with expertise in the disease (MDS and leukemia), histopathology, patient advocacy, ethics, statistics, cohort studies and biorepositories. The OSMB will provide annual safety oversight consistent with NHLBI policy (http://www.nhlbi.nih.gov/research/funding/human-subjects/data-safety-monitoring-policy).

2. Objectives

We hypothesize that it is possible to identify subgroups of patients with MDS with unique clinical, genetic and epigenetic features that are associated with distinct natural histories. Therefore, the specific aims of this study are:

1. To develop a high-quality clinical database containing clinical history, including environmental exposure history, presenting signs and symptoms, diagnostic testing results, co-existing diseases, therapies and response to therapies, disease progression, quality of life and survival.
2. To develop a high-quality biorepository linked to the clinical data that will facilitate diverse studies, including genetic, epigenetic, immunologic, proteomic, and cell-functional and cell-phenotypic studies through the development of (details described further in the Manual of Procedures):
   - Central communication with the biorepository to ensure timely and accurate collections and biospecimen data appended to the clinical database.
   - Defined standard operating procedures for the collection, processing, storage and distribution, with special emphasis on processing protocols fit-for-purpose to sample requirements for downstream testing.
   - Quality management procedures to ensure minimal numbers of errors in the management of the biospecimens.
3. To facilitate broad use of these linked data and specimens to support studies focused on:
   - Improving diagnostic accuracy, risk-stratification and prognostication, and medical decision-making in MDS;
   - Understanding quality of life and its relationship to changing disease and treatment status
   - Understanding the pathogenesis of MDS and diverse MDS subtypes, including genetic, epigenetic, immunologic mechanisms;
   - Optimizing treatment strategies for specific subtypes of MDS;
   - Identifying novel biomarkers for MDS outcomes; and
   - Identifying novel targets for therapeutic interventions in MDS.

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2.1 Potential Studies

The following are described as potential studies and analyses that could be performed from the study materials. They are not specific study hypotheses but show the potential uses for the developing clinical and biologic sample set collected under the study. While individual gene constructs may be mentioned, it should be understood that alternative targets may be identified at later times which might be substituted in the comments that follow. Additional discussion of power or detectable alternatives is included in Section 7. Examples of potential studies include:

- **Detecting improved prognostic factors in low risk MDS**

  The International Prognostic Scoring System (IPSS) provides a risk-based classification method for patients with MDS. The risk of evolution to AML and overall survival for an MDS patient is associated with their IPSS-risk category [low (33% of unselected MDS patients), INT-1 (38%), INT-2 (22%), and high-risk (7%)]. The current prognostic system cannot distinguish the 19% of low-

risk patients that will die with leukemia from those that will not. The substudy can test whether incorporating the mutational status of single genes can improve the ability to predict who will die with AML in the low-risk group.

- **Detecting markers of improved response to hypomethylating therapy**

  Several studies have demonstrated an association between TET2 mutations and an increased likelihood of responding to a hypomethylating agent. Whether additional mutations influence this association remains unproven.

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  Out of a cohort of approximately 1750 suspected MDS patients, we anticipate that up to 500 higher risk MDS patients will receive hypomethylating therapy. Sub group analysis could then be performed for patients with TET2 + other mutations like ASXL1 (occurs in 20%), DNMT3A (occurs in 15%), or one of the frequently mutated splicing factors (cumulatively occur in 50%).

- **QOL and anemia therapy**

  Do transfusions improve QOL for MDS patients with moderate anemia? Do erythropoietin stimulating factors? The study can identify transfusion independent individuals with entry hemoglobin within designated limits. Six month changes in QOL scores can be examined in those Individuals receiving interventions such as transfusions or erythropoietin.

- **Genetic factors in patients with complex karyotype**

  Complex karyotypes, defined as three or more chromosomal abnormalities, have long been associated with increased disease risk and shorter overall survival and are observed in 10% of MDS patients. Recent studies suggest that this association with prognosis might be refined by considering the nature of the chromosomal abnormalities present (e.g., monosomies), the absolute number of abnormalities (e.g., 3 vs. 4. vs 5 or more), or the presence of somatic mutations. Approximately 50% of MDS patients with complex karyotypes will carry a mutation of TP53.

- **Prognostic significance of SF3B1 in MDS patients with Refractory Anemia with Ring Sideroblasts (RARS)**

  Among the genes recurrently mutated in MDS, only mutations of SF3B1 have been associated with a longer median survival. Whether this finding is independent of known prognostic features and disease subtypes is unclear.

3. Selection of Patients

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3.1 Eligibility

- 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**

Rev. Add5

- Diagnosed with de novo or therapy-related MDS within 12-months of enrollment per the World Health Organization (WHO) criteria[1] 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

[1]See Appendix III for WHO peripheral blood and bone marrow findings in MDS.

In participants with suspected MDS and prior to registration with subsequent bone marrow evaluation, alternative causes for the cytopenias should be considered (e.g., internal bleeding, autoimmune cytopenias, thyroid disorders, other causes of anemia etc.). In select individuals, the following tests could be performed to assist in the diagnostic work-up. These evaluations are not required

by the protocol; however, abnormal results in advance of enrollment may reduce the number of non-MDS cases.

- Copper, serum level
- Direct Antiglobulin Test
- Antinuclear Antibody (ANA) Test
- Creatinine
- Calculated Glomerular filtration rate (GFR)
- Thyroid-Stimulating Hormone (TSH) tests performed in prior 6 months

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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 (described in Section 5.1) of the protocol) 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 approximately 1000 participants assigned to the longitudinal cohort. Sample and data collection will cease at baseline for all cases assigned to the cross-sectional cohort. Submitted samples will be reviewed by a central pathologist to determine eligibility for the longitudinal cohort (i.e., an MDS, MDS/MPN, AML with < 30% blasts without core binding factor or acute promyelocytic leukemia, or ICUS diagnosis). Should a discrepancy in diagnosis occur between the central review and study site, the study site will be notified to allow for additional information to be submitted to clarify the diagnosis. Such notifications will not occur in real time, and are not intended to assist in patient care. Additional central sequencing of selected genetic targets will be performed.

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.

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Rev. Add4
Rev. Add5

4. Registration Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>.

For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

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 patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number

- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

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
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol # NHLBI-MDS
- Click on LPO Documents, select the Site Registration Documents link, and download and complete the forms provided.

Requirements for NHLBI-MDS Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Protocol, Biospecimen Acquisition, Biospecimen Shipping, GlobalTrace, and Medidata Rave Training
- For all sites, Central Laboratory/Biorepository registration processes are required including the following:
  1) Identification of at least one member of the study staff certified with IATA or equivalent training to ship biological substances, and
  2) Completed CL/B information Checklist

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 3000
Philadelphia, PA 19103

Institutions with patients 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.

Required Protocol Specific Regulatory Documents

1. 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.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - 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

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- 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
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Study Samples should not be collected prior to registration.

Patient 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>) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient 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. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients 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 registration. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Protocol Number

4.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID
- Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.5 Additional Requirements

4.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

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4.5.2 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

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Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

5. Study Design

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5.1 Data Collection Plan – Clinical Assessments

Enrollment Procedures

- Informed consent will be obtained for data and sample collection.
- Patient histories will be obtained and medical records will be reviewed to obtain past medical history, baseline laboratory tests, diagnostic information including pathology reports and treatment history.
- Bone marrow and peripheral blood slides will be centrally reviewed by study hematopathologists.
- Participants will be required to contribute blood and bone marrow samples for storage.
- Participants will be required to provide eyebrow hairs and a buccal swab at baseline.
- If a sample is destroyed or un-usable, we may attempt to re-contact some participants for additional samples. Failure to participate in the repeat test will not impact their participation in this trial or care and treatment in any way.
- Based on central pathology review a baseline classification into the longitudinal cohort of cases (MDS; MDS/MPN overlap disorder; AML with < 30% blasts without core binding factor or acute promyelocytic leukemia [AML with < 30% blasts including chromosomal rearrangements between chromosomes 8 and 21 and within chromosome 16 as well as t(15;17)]; 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.

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The at-risk longitudinal subcohort will include those cases with at least one of the following:

- Local or central pathology assessments of dysplasia in baseline bone marrow aspirate;
- Any clonal abnormality by conventional karyotype (the abnormal chromosomes must be demonstrated by the routine 20 metaphase cytogenetic analysis, not by fluorescence in situ hybridization [FISH] or sequencing technologies).
  - Examples include +8, del(9p), del(12p),+19, del(20q) or –Y
  - Of note, MDS-defining recurrent chromosomal abnormalities by WHO 2016[112] (Appendix III) are categorized into the longitudinal cohort per WHO guidelines for diagnosis of MDS in setting of cytopenias. These chromosomes include: (inv(3)/t(3q)/del(3q), del(5q), -7, del(7q), del(11q), -13, del(13q), i(17q), +19, del(20q), -Y, t(2;11)(p21:q23), t(3;21)(9q26.2;q22.1), t(6;9)(p23;q34), t(11;16)(q23;p13.3), t(1:3)(p36.3;q21.2);

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- Locally or centrally detected genetic mutations meeting minimally acceptable criteria for allelic variant presence *(ASXL1, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CEBPA, CSF3R, CUX1, DDX41, DNMT3A, ETNK1, ETV6, EZH2, FLT3, GATA2, GNAS, GNB1, IDH1, IDH2, JAK2, KIT, KMT2A, KRAS, MPL, MYD88, NF1, NPM1, NRAS, PHF6, PPM1D,*

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PRPF8, PTPN11, RAD21, RUNX1, SAMD9, SAMD9L, SBDS, SETBP1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, STAT3, STAT5B, TET2, TP53, U2AF1, WT1, ZRSR2)

- No post baseline biological samples or data will be captured for those classified into the cross-sectional cohort .
- 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 acute promyelocytic leukemia, or ICUS after the relevant category-specific sample size limits have been reached.
- Sites will be notified by an email message, no later than the 12th month post-enrollment, when longitudinal follow-up is required. Individuals not assigned to the cross-sectional group by month 6 should submit specimens and data associated with the 6 month visit. The electronic case record for the individual will also be modified.
- Capture of biologic samples will be discontinued if the participant receives an HCT. Additional data may be collected from the CIBMTR on patients receiving a transplant.
- Biologic samples are submitted for cases in the longitudinal cohort at the time of AML diagnosis (i.e., blasts >30% and >=50% increase from baseline). Subsequent samples will not be collected for AML cases.
- Individuals may participate in other studies but will continue to submit data and specimens for this protocol.

5.2 Detailed Protocol Procedures

5.2.1 Standard Diagnostic Procedures at Baseline

The objectives for collection of these results are for the diagnostic classification, assessment of severity and determination at the point of entry on the study. The tests may be performed to exclude most common disorders that can mimic MDS, including but not limited to systemic diseases and vitamin deficiencies, or overlap with MDS such as Aplastic Anemia (AA), Paroxysmal Nocturnal Hemoglobinuria (PNH), Large Granular Lymphocytic (LGL) leukemia, Acute Myelogenous Leukemia (AML), Amegakaryocytic Thrombocytopenic Purpura, etc. Some of the tests can be used specifically if a diagnosis of an individual disease, based on a strong clinical suspicion, has to be confirmed. Blood and marrow will be taken only at the occasion of medically indicated **diagnostic testing**. The diagnosis will be established based on clinical grounds and in accordance with the definitions provided in Appendix III.

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Following procedures described in the MOP, study group assignment will be determined by a study-associated hematopathologist to classify each participant into the longitudinal cohort of cases (MDS, MDS/MPN overlap disorders, AML with < 30% blasts without core binding factor or acute promyelocytic leukemia, or ICUS) and the cross-sectional cohort (all others).

5.2.1.1 Medical History and Physical Examination

The following information will be recorded at the time of enrollment with the baseline study visit:

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1. Demographics
2. Site diagnosis
3. Blood counts and bone marrow assessment
4. Past medical history
5. Physical examination
6. Past year medications
7. QOL
8. Hospitalizations/ICU admissions
   a. Dates
   b. Reasons
9. Transfusions
   a. Dates
   b. Number of units
10. Infections requiring antimicrobial therapy
11. Environmental exposures
12. Screening Frailty assessment using the **VES-13**[107] (13 item questionnaire completed by the patient). While no instrument alone has been shown to be a substitute for comprehensive geriatric assessment by a geriatric physician, the VES-13 has been successfully used in several cancer-related studies[108] and others to provide basic screening for frailty, including for patients with blood cancers in need of stem cell transplant.[109]

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13. Charlson Comorbidity Index
14. Novel Coronavirus Disease 2019 (COVID-19) Evaluation

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5.2.1.2 Standard Diagnostic Laboratory Evaluation

All participants at baseline must have:

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

The following laboratory evaluations may be performed, but are not required for the protocol. Data should be submitted when available:

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

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9. Rheumatoid Factor
10. T cell receptor (TCR) gamma/beta 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

5.2.1.3 **Specialized Laboratory Testing**

Procedures are provided in the Manual of Procedures (MOP) with regard to collection, processing, assays, labels, shipping, storage, and retrieval, aliquoting, destroying and maintaining biospecimens. SOPs for bone marrow and peripheral blood processing that meet national guidelines and quality assurance processes are maintained by the Central Laboratory for the study. The CL/B is College of American Pathologists accredited.

5.2.2 Procedures at Follow-up

5.2.2.1 **Medical and Physical Examination**

The following information will be recorded at follow-up visits every 6 months for participants not assigned to the cross-sectional cohort:

1. Disease evaluation
2. Physical examination
3. MDS therapy
4. Transplant status
5. Hospitalizations/ICU admissions
   a. Dates
   b. Reasons

6. Transfusions
    a. Dates
    b. Number of units
7. Frequency of infectious complications

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8. Adverse events
9. Concomitant therapy
10. QOL
11. Malignancy
12. Survival status

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13. COVID-19 Evaluation

5.2.2.2 **Laboratory evaluations during follow-up**

For all participants not assigned to the cross-sectional cohort, follow-up visits every 6 months will include:

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

Peripheral blood should also be obtained when it is suspected that a patient has evolved to AML (i.e. blasts > 30% and >=50% increase from baseline), and whenever a bone marrow aspiration is performed.

In addition, the following procedures may be performed as needed per standard of care. Bone marrow samples and/or 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

5.2.3 Types of specimen and quantities

Procedures will be followed based on the manual of operations (MOP) and in accordance with the site-specific plan for the collection of biological material.

5.2.3.1 **Peripheral Blood:** 34.2 ml of blood is requested at each sampling point. 20 ml in green top (sodium heparin) tubes, 3 ml in red top tube, 8.7 ml in PAXgene DNA Extraction tubes, and 2.5 ml in PAXgene RNA extraction tube. Samples are required at entry and every 6 months subsequently. They should also 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.

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From these tubes the following cellular products will be generated for storage at the CL/B until the conclusion of the study followed by transfer to the NHLBI for long-term storage:

- Cryopreserved peripheral blood mononuclear cells
- Serum
- Genomic DNA
- Total and microRNA

5.2.3.2 **Bone marrow biopsies and 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. Whenever a bone marrow aspirate is performed, 13 ml of bone marrow aspirate is requested: 5-10 ml in a tube containing sodium heparin, and 3 ml in a tube containing EDTA. Only 1st or 2nd pulls should be submitted.

From these tubes of bone marrow aspirate the following products will be created and stored at the CL/B for the duration of the project and then deposited in the NHLBI biorepository for long-term storage.

- Cryopreserved cells
- Purified CD34+ cells

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- BM smears
- Bone marrow plasma
- Frozen cell pellets
- Purified DNA

5.2.3.3 **Germline Control for Genetic Testing**

Multiple somatic mutations have been identified in MDS. For accurate genetic description and somatic assignment, non-hematopoietic contaminated germline DNA is required as a control. Hair follicles and buccal swabs will be required at baseline and then optionally collected at 12 and 24 month visits.

- **Hair Follicles:** Six hairs will be plucked from each eyebrow (12 eyebrow hairs in total) using a sterile pair of tweezers and gloves. Hair from the hairline may be submitted instead of or as a supplement to the eyebrow hair. The follicle must be obtained. Hairs with attached follicles will be placed in a transport tube without transport medium and shipped to the CL/B for DNA extraction.

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- **Buccal Swab:** Buccal cells will be collected by rubbing the inside cheek of the mouth with 2 sterile swabs. The buccal swab will be placed in sterile packaging and shipped to the CL/B for DNA extraction.

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5.2.4 Storage of specimens

- Research materials, including biospecimens and data collected as part of the Study, will be delivered to the NHLBI to be used as a scientific resource by the research community. NHLBI will serve

as the custodian of the scientific resource and will distribute materials to qualified investigators with approved research protocols as described in the Biologic Specimen and Data Repositories Information Coordinating Center Handbook at www.biolincc.nhlbi.nih.gov. The distribution of materials will follow all Federal, State, and local statues and regulations.

- Linked/Coded: bone marrow aspirates, peripheral blood specimens and pathology material will be shipped for receipt at the CL/B. Individual personal identifiers will not accompany the samples to protect confidentiality.
  - The clinical study personnel, PI, or the PI's representative, will track the specimen shipments within GlobalTrace (See MOP for instructions). Information recorded with the specimen will include the date of collection and associated processing information.
  - The specimens will be labeled with unique codes that do not contain patient identifying information and have been pre-assigned to the site by the CL/B. Representatives from the study team will provide the exact codes. The link to the code is stored at the Data and Coordinating Center for The National MDS Study and will link the specimens to the clinical data collected on this study. Only relevant clinical data will be shared with researchers requesting samples and data for research purposes. No identifying information will be shared.

NOTE: There will be no specific information that an outside source can link to the specimen stored at the CL/B. Since the code will be maintained in a secure location and generated with unique codes issued by the NHLBI representatives, it will NOT be possible for someone to break the code and link specimens directly to a participant's clinical record. No information will be shared outside of the immediate research team. Confidentiality will be maintained at all times by following ethical procedures for the protection of subjects participating on research protocols.

5.3 Adverse Event Reporting Requirements

As this study is observational, no treatment related adverse experiences are attributable to study therapy. Severe adverse events related to study acquired biologic samples will be recorded on study report forms.

5.4 Quality of Life Administration

5.4.1 Instruments to be Administered

The study will perform assessments of QOL using the MDS-specific QUALMS, the FACT-G (Version 4), the PROMIS Short Form v1.0 – Fatigue 7a and the EQ-5D-5L.

5.4.2 Assessment Schedule

QOL instruments will be administered at baseline, month 6, 1 year and yearly, thereafter, (see Table 4 in Section 6).

These patient-reported outcome assessment time points correspond to standard clinic office visits of routine care to minimize participant burden.

5.4.3 Administration

5.4.3.1 The questionnaires must be administered at the time points listed above. The patient should be instructed to respond to the questionnaires in terms of his/her experience during the timeframe specified on each questionnaire.

5.4.3.2 The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the completion of the questionnaires as long as the staff person does not influence the patient's responses.

5.4.3.3 The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately.

- If more than one answer was marked, the patient should be asked to choose the answer which best reflects how he/she is feeling.
- If a question was not answered, the patient should be asked if she would like to answer it. The patient should always have the option to refuse.
- If the patient refuses, it should be indicated on the questionnaire that he/she declined to answer the item.

5.4.3.4 If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be noted according to the instructions in the NHLBI-MDS Forms Completion Guidelines.

5.5 Duration of Study

Patients will participate on this study unless:

- Hematopoietic cell transplantation occurs. Capture of biologic samples will be discontinued if the participant receives an HCT. Vital status follow-up will continue but other post-transplant data will be captured by the CIBMTR national registry.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, collection of additional data and samples should be discontinued. In this event submit data through Medidata Rave according to the schedule in the NHLBI-MDS Forms Completion Guidelines.
- Patient withdraws consent.

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6. Study Follow-Up Schedule

6.1 Overview of Study Procedures for all Enrolled Participants

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TABLE 4: 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 Thyroid-Stimulating Hormone (TSH) tests performed in prior 6 months iron studies (iron, Total Iron-Binding Capacity (TIBC), percent saturation),	X[7]								
Charlson Comorbidity Index	X								
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]
Bone Marrow Aspirate Sample Shipment (detailed in Section 5.2 and in MOP)	X	X							
Peripheral Blood Sample Shipment (detailed in Section 5.2 and in MOP)	X	X[2,3]	X	X	X	X	X	X	X
Slides for Central Pathology Review (detailed in Section 8.1 and in MOP)	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. 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.
4. Germline DNA will be extracted by the CL/B from the following materials: eyebrow follicles and buccal swabs. The eyebrow follicles and buccal swabs are required at baseline, and may be optionally provided at 12 and 24 months.

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5. Post baseline, MDS cases and AML cases with <30% blasts without core binding factor or acute promyelocytic leukemia complete the 4 questionnaires. Cases entered with ICUS or in the at-risk cohort complete only the PROMIS Short Form v1.0 – Fatigue 7a and EQ-5D-5L. After one year, the QOL instruments are completed annually.
6. Biological Sample Submissions
7. If the patient is anemic, these tests should be performed in the prior 6 months.

Biological Materials to be Collected and Shipped to CL/B

Submission of pathologic/biological materials for review and classification is mandatory in order for the patient to be considered evaluable. Failure to submit the requested materials may render the case unevaluable.

Samples must be submitted for analysis to determine patient eligibility as outlined in Section 5.2. The biological materials will be used as described in Section 5.2.3.

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TABLE 5: The National MDS Study Sample Submission Schedule

Material	Baseline	Collected when medically indicated aspiration performed	Every 6 months during follow-up (samples to be submitted ± 60 days from the target visit dates)	At 12 and 24 months	**Suspected progression to AML blasts >30% and >=50% increase from baseline**	**Ship To:**
Bone marrow (5-10 mL in a tube with sodium heparin)[1]	X	X				Central Lab/Biorepository (See MOP for address)
Bone marrow (3 mL in a purple top tube with EDTA)[1]	X	X				
Germline tissue (12 eyebrow hairs with follicles; 6 hairs from each eyebrow and 2 buccal swabs)[3]	X			X		
Peripheral blood (2X 10 mL in heparin sodium tubes)[2]	X	X	X		X	
Peripheral blood (3 mL in red top tube)[2]	X	X	X		X	
Peripheral blood (8.7 mL in PAXgene DNA extraction tube)[2]	X	X	X		X	
Peripheral blood (2.5 mL in PAXgene RNA extraction tube)[2]	X	X	X		X	
Pathology Slides (Detailed in Section 8.1 and in MOP)	X	X[1]				

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

2 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.

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

7. Statistical Considerations

7.1 Study Size

As stated in the objectives, this study intends to develop a longitudinal cohort of clinically characterized MDS and ICUS cases with an associated set of biorepository specimens to support multiple basic science, clinical and epidemiologic research studies. As such, a single hypothesis driving a particular statistical comparison does not exist and the selected sample size is instead consistent with pragmatic issues and useful scientific objectives.

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At the time of study design, it was anticipated that approximately 2000 confirmed MDS cases and 500 ICUS cases would be enrolled based on the eligibility and exclusion criteria in the protocol. Power calculations were performed around these sample size assumptions with the understanding that there were uncertainties in rates of accrual and follow-up as well as in the distribution of disease subgroups. These calculations are retained in Section 7.2.

Since designing this study, several factors contributed to reducing the size of the study from what was planned originally. These factors include a slower than anticipated rate of enrollment (gleaned from the vanguard phase that included the first 200 participants), the distribution of disease subgroups of the enrolled participants following central histopathology review, fiscal constraints, and also

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the unforeseen impact of the COVID-19 pandemic on the study. As a result, in Addendum #7, the study size was decreased such that approximately 1750 participants with suspected or newly diagnosed MDS would be enrolled and would contribute specimens to the biorepository. It was anticipated that approximately 500 of the 1750 participants to be enrolled would be confirmed MDS cases. However, based on current enrollment rates and the distribution of disease groups, it is anticipated that approximately 2000 participants would be required to be enrolled so that the final biorepository would consist of 500 confirmed MDS cases. As detailed below, with a projected sample size of 500 confirmed MDS cases, the study would have:

- 80% power in detecting a baseline prognostic factor present in 25% of confirmed MDS cases (such as presence of high clonal count subpopulations) that is associated with a minimum 12% decrease in mortality when the 5-year mortality rate is at least 20%.
- Estimated 95% confidence interval widths between 5.3% and 8.8% for event rates (such as progression to AML) that range from 10% to 50%, respectively.
- 80% power in detecting correlation coefficients as low as 0.13 for evaluating the baseline associations between continuous variables (such as whether hemoglobin values are correlated with differences in QOL), with a maximum 95% confidence interval width of 0.17.

7.2 Original Study Considerations

A study with 2000 MDS cases will provide the ability to detect with high power covariates that discriminate between prognostic subgroups. It is anticipated that the 5 year mortality rate in this group will be approximately 50%. Uniform enrollment over the 6 year study period and a drop-out or loss-to-follow-up rate of <=2% per 6 months is planned. The study has 87% power to detect a baseline

factor present in 25% of the individuals when the factor is associated with a 20% (i.e. 10% point) decrease in the 5 year mortality rate. As examples, if the upper quartile of the HQL population as measured by the QUALMS have improved survival results at the level indicated in the first line of the table below, this effect should be detectable in the study. Similar power would be applicable to a test of low versus high clonal count subpopulations or other potential prognostic indicators evaluated in studies of assays of the MDS group. The table also demonstrates that for phenotype subgroups of 500 (by examining, for example a restricted age class, those with a particular WHO classification or those with defined entry comorbidities) larger differences in mortality rates for the prognostic categories would be required to achieve adequate power.

Power for detecting survival distribution differences (proportional hazards) using 2 tail 5% level test in a study with uniform accrual over a 6 year total study period with semiannual follow-up losses of 2%

Power %	N Group 1	N Group 2	Group 1 5 Year Mortality %	Group 2 5 Year Mortality %
87	1500	500	50	40
31	375	125	50	40
88	375	125	50	30

In the ICUS group of 500 total patients, one might evaluate whether presence of clonally restricted somatic mutations or alternative potential prognostic factors can be identified as predictors of mortality or progression to MDS. For this endpoint, we anticipate the 5 year event rate to be near 25%. The following table shows that relatively common prognostic factors associated with an absolute 15 percentage point difference would be detectable with greater than 80% power.

Power for detecting differences (proportional hazards) in ICUS individuals dying or developing MDS using 2 tail 5% level test with uniform accrual over a 6 year total study period and semiannual follow-up losses of 2%.

Power %	N Group 1	N Group 2	Group 1 5 Year Mortality/MDS %	Group 2 5 Year Mortality/MDS %
83	375	125	25	10
88	125	375	25	10

The selected sample size will provide for calculation of estimates with associated precision some of which are described below. For event rates (for example, development of AML or transfusion use in the year post initiation of a specific therapeutic regimen) the following table describes the 95% confidence interval half-widths for selected sample sizes and observed event rates.

Event Rate Precision characterized by Asymptotic 95% Confidence Interval Half Widths for Selected Sample Sizes and Event outcome rates.

Sample Size	Event Rate		
	.1	.25	.50
2000	.013	.019	.022
700	.022	.032	.037

500	.026	.038	.044
100	.059	.085	.098
50	.083	.120	.139

With continuous variables, correlation coefficients can be computed. The sample sizes required to have precise, as measured by specified half-widths of the 95% confidence interval for selected Pearson correlation coefficients, are detailed in the table that follows. For this fixed precision requirement the sample size requirement is sensitive to the correlation value. From the table below, one would likely want to select a sample of approximately 200 cases to evaluate, for example, whether changes in hemoglobin values have important correlation with quality of life score changes. Similar consideration would apply to correlation studies of bioassay results with continuous outcomes from repository samples.

Pearson Correlation Coefficient, sample sizes required for 95% Pearson Confidence intervals with designated interval half-widths.

Correlation	CI half-width =.05	CI half-width =.1
.2	1417	355
.5	867	219
.8	205	56
.9	62	20

The DNA resource created by this proposal would not be of sufficient size for a stand-alone GWAS discovery study, but it could contribute as an independent study population for candidate gene validation studies or for validating 'hits' from GWAS discovery studies. The available sample size could be sufficient for candidate gene validation studies of common variants and common phenotypes. Suppose that development of a particular outcome (such as development of MDS) is of interest in some phenotype group (e.g. ICUS participants). The table below shows the detectable (with 80% power) event rate in the minor allele frequency (MAF) SNP group when the event rate is .1, .25 or .5 in the other group. A two-sided 5% level test is performed for varying numbers of SNPs and two MAF levels while searching for lower event rates in the less common group. Note that large increases in event rates are detectable in the MAF group even for the smaller sample sizes, for example the detection limits for the first 3 elements in row 1 would be .26, .31 and .36, if upper detectable event rates were tabled.

Lower detectable event rates in MAF group with 80% Power, 5% level Bonferroni adjusted test.

N	Event rate in non-MAF group	**10% MAF**			**20% MAF**		
		1 SNP	**10 SNPs**	**100 SNPs**	**1 SNP**	**10 SNPs**	**100 SNPs**
250	.1	ND	ND	ND	ND	ND	ND
500	.1	.003	ND	ND	.02	.002	ND
1000	.1	.02	.005	ND	.04	.03	.01
250	.25	.04	ND	ND	.08	.04	.003
500	.25	.09	.04	.01	.13	.09	.06
1000	.25	.13	.10	.07	.16	.13	.11

N	Event rate in non-MAF group	10% MAF			20% MAF		
		1 SNP	**10 SNPs**	**100 SNPs**	**1 SNP**	**10 SNPs**	**100 SNPs**
250	.5	.22	.14	.08	.28	.22	.17
500	.5	.30	.24	.19	.35	.30	.26
1000	.5	.35	.31	.28	.39	.36	.33

ND-Event rate > 0 is not detectable with 80% power

The significance of the study results will be interpreted in light of the multiplicity issues inherent in the conduct of a longitudinal study with multiple medical evaluations and biological samples over time. To deal with multiplicity, thresholds for the significance of p-values will be more stringent than the traditional 0.05 cutoff, as appropriate.

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7.2.1 Comments on Potential Substudies

For each of the potential substudy scenarios identified in Section 2.1, additional discussion is provided to describe power and detectable alternatives based on the sample size specified in the original study considerations in Section 7.2. When applicable, accrual rate, drop out and study length assumptions are the same as used previously in this section.

- **Detecting new prognostic factors in low risk MDS**

  We expect that a study with 2000 MDS cases will have 660 (33% of all MDS patients) low-risk patients. We estimate that these low-risk patients will have a 19% 5 year rate of death with leukemia. For a single low frequency gene (5% mutation rate) the study has 80% power to detect a gene associated with a 45% mortality rate. Additional type 1 error rate adjustment would be required if a set of genes are being explored.

- **Detecting markers of improved response to hypomethylating therapy**

  Among 500 higher risk MDS patients who receive hypomethylating therapy, about 250 should respond to treatment while another 250 will show no benefit. Further a TET2 mutation rate of 20% is expected. When the common gene subgroup has a response rate of 45%, we can compute the detectable alternative under a 2 sided 5% level hypothesis test to be 61%. The subgroup with frequently mutated splicing factors has a cumulatively occurrence of 50%. Comparing TET2 mutant patients with a second mutation to TET2 mutant patients without a select second mutation would give 80% power to detect a 25-30% difference in response rate, e.g. 40% versus 67%.

- **QOL and anemia therapy**

  The FACT-G has a within person standard deviation of approximately 10. A mean change score difference of 5 approximates that observed in individuals who have temporal changes in performance status class. With this detectable

difference 175 individuals equally split between 2 groups provide 90% power.

- **Genetic factors in patients with complex karyotype**

  A cohort of 2000 MDS patients will be expected to have 200 with a complex karyotype, 100 of which should carry mutations of TP53. This substudy will have high power to detect large differences in median survival time, e.g. 86% power to detect a difference between median survival times of 2 and 3.8 years.

- **Prognostic significance of SF3B1 in MDS patients with Refractory Anemia with Ring Sideroblasts (RARS)**

  SF3B1 mutations can be found in approximately 20-25% of patients with MDS, about half of which will have the RARS subtype. We expect that with 2000 MDS patients, we will have 400 with mutated SF3B1 of which 200 will have RARS and 200 will have other MDS subtypes. In addition, there should be another 40 RARS patients without SF3B1 mutations. This study would have adequate power only if differences in underlying survival distributions are large, e.g. 84% power to detect median exponential survival differences of 2.8 years versus 6.8 years in the SF3B1 mutation group.

7.2.2 Additional Analysis Considerations

There are multiple subgroups of special interest in this cohort including individuals with therapy-related MDS and those with MDS/MPN overlap disorders. Each group may comprise up to 10% of the cohort. Individuals will be included/excluded from select substudies depending on the substudy focus. General questions from earlier discussions will be applicable to these individuals as attempts to elucidate the importance of genetic factors, quality of life changes and other issues are explored.

Along with selection and other biases that are applicable in cohort studies, the analysis of specific substudies will consider the impact of informative censoring. This is a potential issue in many studies of MDS patients since they are often elderly and have additional comorbidities. Note that many of the studies may have mortality endpoints and informative censoring for these can only occur when there are dropouts from mortality endpoint ascertainment. We expect that this loss to follow-up rate will be small which in itself limits the potential impact of informative censoring and, as always in studies performed under the auspices of the NCTN, we will work towards limiting this problem. The approaches to mitigating the impact of informative censoring will depend on the outcome of interest and the study design. At times, the endpoint can be redefined to lessen the risk of inferential error attributed to informative mortality censoring (e.g. use endpoint of time to progression or death rather than to progression). Consideration of competing risks and/or use of multistate models can be used and inference results examined in light of the simpler versus more complex model implications. In general stratifying by covariates correlated to the censoring factor can provide insight and in repeated measures analyses, stratification by

missingness pattern can be useful in mitigating impact of informative censoring. The challenge is that it is not easy to examine the randomness assumption required for unbiased inference. Strategies for exploring this issue typically involve introducing sensitivity analyses often after parameterizing a distributional shift (bias) that occurs when censoring is not random. These approaches often rely on the principal stratification framework applicable when evaluating causal estimates. This approach can be applicable if a continuous outcome measure is available in the responder subgroup.

Some of the study objectives require an analysis of longitudinal data with heterogeneity of personal trajectories. Analysis of repeated measurement data using growth curve models and estimation using the Generalized Estimating Equations (GEE) approach will likely be employed in some analyses. Health and Quality of Life (HQL) will be evaluated at each time point and summarized using simple descriptive statistics (e.g.mean, SD). When group differences are posited, models will be adjusted for baseline HQL. Partly conditional regression, conditioning on being alive at each time point, can be used to compare the longitudinal HQL measurements over time between the groups.[110] Interactions with time will be tested for and if significant, group effects will be estimated separately for each time point. The missing data pattern of the HQL measurements will be examined using graphical techniques and logistic regression models conditional on survival. At each time point, estimates of the difference in HQL between the groups conditional on survival at that time point will be obtained using inverse probability of censoring weighted GEE with independent estimating equations[111] to account for missing data.

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In response to the COVID-19 pandemic, the study is collecting data on the COVID-19 status (positive or negative), hospitalizations and medications received due to COVID-19. Also, the study is implementing a way to track protocol deviations associated with COVID-19. Several aims can be explored with the addition of the COVID-19-related data points. These may include evaluation the effect of COVID-19 on the study endpoints such as mortality, progression to AML, and hematopoietic stem cell transplantation.

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8. The National MDS Study Pathology Review

Diagnostic material from baseline must be submitted for review and classification by the study. Diagnostic material will be centrally reviewed at baseline for all enrolled cases and post-baseline for any cases where additional diagnostic bone marrow samples are collected.

The submitting pathologist and clinical research associate should refer to the MOP for additional guidelines.

8.1 Materials Required For This Protocol

8.1.1 Electronic case record and associated data forms

8.1.2 Pathology information and a copy of the surgical pathology report will be submitted through the data capture system. In addition all information available on karyotype, FISH and molecular genetic studies that have been performed at the home institution, will be collected.

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8.1.3 Required Diagnostic and Classification Material

8.1.3.1 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 slide is required if biopsied
- 1 unstained core section is required if biopsied

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- 1 touch preparation slide is required if dry tap occurs

8.1.3.2 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 slide is required if biopsied
- 1 unstained core section is required if biopsied
- 1 touch preparation slide is required if dry tap occurs

NOTE: Submission of pathologic materials for diagnostic review is mandatory in order for the patient to be considered evaluable. Failure to submit pathologic materials may render the case unevaluable.

8.2 Shipping Procedures

8.2.1 Submission Schedule

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8.2.1.1 All blood and bone marrow samples should be shipped on the date of collection for receipt at the CL/B within 24 hours. Samples collected on Friday must be sent for Saturday delivery. Refer to the MOP for specific shipping instructions.

8.2.1.2 The required slides for central hematopathology assessment must be submitted within 7 days of aspiration procedure. Refer to the MOP for specific shipping instructions.

8.2.2 Shipping Address

Refer to MOP for shipping address and instructions.

9. Electronic Data Capture

Please refer to the NHLBI-MDS Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

10. This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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The National Myelodysplastic Syndromes (MDS) Study

Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials or studies, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

The National Myelodysplastic Syndromes (MDS) Study

Appendix II

World Health Organization (WHO) 2008 Peripheral Blood and Bone Marrow Findings in MDS*

Disease	Blood findings	Bone marrow findings
Refractory cytopenia with unilineage dysplasia (RCUD): [Refractory anemia (RC); Refractory neutropenia (RN); Refractory thrombocytopenia (RT)]	Unicytopenia or bicytopenia[1] No or rare blasts (< 1%)[2]	Unilineage dysplasia: > 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)[2] No Auer rods < $1x10^9$/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ± 15% ring sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts[2] No Auer rods < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 5-9% blasts[2] No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5-19% blasts[3] Auer rods ±[3] < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 10-19% blasts[3] Auer rods ±[3]
Myelodysplastic syndrome – unclassified (MDS-U)	Cytopenia(s) < 1% blasts[2]	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS < 5% blasts
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

Table from Reference 24

*Refer to the most recent WHO definitions for diagnosis.

1. Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS- U.
2. If the marrow myeloblast percentage is less than 5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB 1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.
3. Cases with Auer rods and < 5% myeloblasts in the blood and < 10% in the marrow should be classified as RAEB-2. Although the finding of 5-19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have less than 5% blasts in the blood if they have Auer rods and/or

10-19% blasts in the marrow. Similarly, cases of RAEB-2 may have less than 10%blasts in the marrow but may be diagnosed by the other two findings, Auer rod+ and/or 5-19% blasts in the blood.

Definitions

- Myelodysplastic Syndrome diagnosis

  Myelodysplastic Syndrome is the primary disease to be studied in this project. It is defined by peripheral blood cytopenias with dysmyelopoietic bone marrow for which no other discernible cause exists. The term dysmyelopoietic refers to qualitative (and quantitative) abnormalities of the three cell lines (dyserythropoiesis, dysgranulomonopoiesis and dysmegakaryocytopoiesis). Because these findings alone are not diagnostic of MDS, potentially contributing conditions must be excluded. Nutritional status, alcohol and drug use, occupational exposure to toxic chemicals, prior treatment with antineoplastic agents or radiotherapy, and risk factors for treatment of human immunodeficiency virus (HIV) infection should be elicited. Since many patients with MDS have macrocytic anemia, folate deficiency must be excluded.

- Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) Overlap Disorders

  The WHO classification of myeloid neoplasms and acute leukemia defines the following myeloproliferative neoplasms that exhibit clinical, laboratory, and morphologic features that “overlap” both MPN and MDS: chronic myelomonocytic leukemia (CMML), atypical (BCR-ABL negative) chronic myeloid leukemia (aCML), and juvenile myelomonocytic leukemia (JMML).

- Idiopathic Cytopenia of Undetermined Significance (ICUS)

  ‘Idiopathic Cytopenia of Undetermined Significance’ is a term used to describe individuals with unexplained persistent cytopenia(s) without the morphologic or cytogenetic abnormalities for a conclusive diagnosis of MDS. Although patients with ICUS do not meet the minimal WHO criteria for MDS, they may progress and develop morphologic or cytogenetic evidence of the disease. The formal definition of ICUS typically requires ≥6 months of observation of cytopenia(s). For the purposes of the initial classification, cytopenia duration can be less than 6 months.

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Appendix III

World Health Organization (WHO) 2016 Peripheral Blood and Bone Marrow Findings and Cytogenetics of MDS

Name	Dysplastic lineages	Cytopenias[1]	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%[2]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%[2]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%[2]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%[2]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM < 5%, PB = 1%,[3] no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM < 5%, PB < 1%, no Auer rods	Any
based on defining cytogenetic	0	1-3	< 15%[4]	BM < 5%, PB < 1%, no Auer rods	MDS-defining abnormality

Name	Dysplastic lineages	Cytopenias[1]	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
abnormality					
Refractory cytopenia of childhood	1-3	1-3	None	BM < 5%, PB < 2%	Any

Table from Reference 112

1. Cytopenias defined as: hemoglobin, < 10 g/dL; platelet count, <100 × 10^9/L; and absolute neutrophil count, < 1.8 × 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be < 1 × 10^9/L
2. If *SF3B1* mutation is present.
3. One percent PB blasts must be recorded on at least 2 separate occasions.
4. Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.