Committee on Clinical Investigation
Children's Hospital Boston

APPLICATION FOR SPECIMEN & DATA REPOSITORY & REGISTRY

This form is to be used to obtain IRB approval to establish specimen and data repositories or registries This includes the storage of human biological specimens and information derived from patient and hospital records. **This form is not intended for use when data or specimens are collected and used for a single specimen or medical record project This form is intended for larger departmental, institutional, or research group-based data and specimen repositories and registries which collect specimens or data for future research by multiple investigators**.

FOR CCI OFFICE USE ONLY	
DATE-STAMPED RECEIVED	**PROTOCOL #**

In addition to this form, please submit a completed **Part D** (financial disclosure) signed by the PI and a completed **Addendum A** (study personnel listing). These forms are available on the CCI website under Info for Researchers >> Forms.

Protocol Number	10-02-0057
Protocol Title	Pediatric Myelodysplastic Syndrome and Bone Marrow Failure Disorder Registry and Tissue Repository

1. Principal Investigator.
There can only be one principal investigator. The PI must assume responsibility for the specimen repository. Non-Children's Hospital personnel and staff may not be principal investigators.

PI's Name	**Inga Hofmann**
PI's Department and Division	**Medicine** and **Hematology/Oncology**
PI's Children's Hospital ID#	**115712**
Phone#/Extension	**617-919-3422**
Pager#/Beeper	**CHB pager # 1238**
Email Address	**inga.hofmann@childrens.harvard.edu**
Office Mailing Address	**300 Longwood Ave, Karp Family Research Building, Karp 8, Boston, MA 02115**

2. Additional Contact.
It is strongly recommended to list the Coordinator or Administrative Contact as this person will receive copies of all pertinent CCI correspondence and notices in addition to the PI.

Additional Contact's Name	**Garce Yoon, MSN, NNP**
Children's Hospital ID#	**124782**
Phone#/Extension	**5-9148**
Email Address	**grace.yoon@childrens.harvard.edu**
Office Mailing Address	**PV 632, Children's Hospital Boston 300 Longwood Ave. Boston MA 02115**

3. Data/Specimen Repository/Registry Name.

Pediatric Myelodysplastic Syndrome (MDS) and Bone Marrow Failure Disorder (BMF) Registry at CHB

4. Data/Specimen Repository/Registry Research Staff and Personnel

List all individuals associated with this protocol in Addendum A: Research Staff and Personnel Form (CCI website, under '*Info for Researchers'*, click '*Forms*'), and attach to this application. You may save Addendum A, update as needed, and re-submit at subsequent continuing reviews.

5. Funding & Grant Information

a. Please provide the requested funding information below.

	Funding Source #1	**Funding Source #2 (if applicable)**
You must select one → Check the type(s) of funding that will be used to conduct the proposed research.	**NO SPONSOR,** explain how study will be conducted w/o funding: _____ ☒ **FEDERAL*** *__New__: Submit 3 copies of entire grant application ☐ **STATE** ☐ **CORPORATE/INDUSTRY** ☐ **EXTERNAL FOUNDATION** ☐ **CHILDREN'S HOSPITAL BOSTON** ☐ Internal Award ☐ Practice/Foundation Funds ☐ Department/Division Funds	**NO SPONSOR,** explain how study will be conducted w/o funding: _____ ☐ **FEDERAL*** *__New__: Submit 3 copies of entire grant application ☐ **STATE** ☐ **CORPORATE/INDUSTRY** ☐ **EXTERNAL FOUNDATION** ☐ **CHILDREN'S HOSPITAL BOSTON** ☐ Internal Award ☐ Practice/Foundation Funds ☐ Department/Division Funds
Sponsor Name * If NIH funded, indicate "NIH' and specify Institute.	**NIH/NIDDK**	
Contact Name, *if applicable*	**William Etti**	
Contact Phone Number:	**301-594-7451**	
Sponsor Address, *for CCI invoice*		
The Sponsor will provide:	☒ **RESEARCH FUNDING** Funding: ☒ committed ☐ pending	☐ **RESEARCH FUNDING** Funding: ☐ committed ☐ pending
Children's Hospital is:	☒ **Primary Institution** ☐ **Subcontract** → Primary Institution is: _____ ☐ **Other:** _____	☐ **Primary Institution** ☐ **Subcontract** → Primary Institution is: _____ ☐ **Other:** _____

b. Are you utilizing ANY CTSA resources in the conduct of this study? ☐ **YES** ☒ **NO**

These services include: Use of space on 6 East, CAT/CR or research space at Waltham

- *Nursing assistance at above sites*
- *Off-site nursing and/or research coordinator services provided through CTSU*
- *Specimen collection or processing, sample storage and preparation for shipping*
- *Assistance from nutritional Metabolic Phenotyping Core (preparation of research meals, analysis of food records, etc.)*
- *Payment of any study-related research costs (patient care expenses, labs, other testing)*
- *Use of specialist equipment located on the CTSU (3DMD camera, DXA, pQCT, V-max, etc.)*

6. Does this protocol involve the establishment of a:

☐ Specimen repository
☐ Data Registry
☒ Both

7. LOCATION OF DATA REPOSITORY/REGISTRY

Specify where the repository/registry will be located? If it is at another site, provide information about the location, agency/location.

The specimen repository will be located in the tissue bank of the Neufeld laboratory, which is located in the Karp Family Research Building on the 8th floor. The tissue bank has designated freezers (-20C, -80C, and liquid nitrogen) and a state of the art bar coding system and inventory tracking system (iLab), which is operated by trained expert staff. Research samples are deidentified and bar code coded. Research sample data are stored on password protected computers in the Neufled laboratory and are backed up through CHB web services. Research investigators and users of the bank will not have access to this freezer and the coded specimens except through Dr. Hofmann and the banking staff. Even the PI has no direct knowledge of the location of specific samples and is required to go through the tissue banking staff in the Neufeld laboratory to retrieve samples. This process will assure that patient research samples will not be retrieved unauthorized without prior approval from the PI.

The associated clinical data will be captured in a unique database specifically built by the Clinical Research Program (CRP) at CHB for this registry. Reseach data will be stored on password protected computers with restricted access and backed up throgh CHB web services.

8. SUBJECT INFORMATION

Data for this repository/registry will be collected from the following types of subjects.
Check all that apply.

☒ Minors/children (age less than 18 years)
☒ Adults (age 18 years or greater)

9. PURPOSE OF REGISTRY/REPOSITORY

Concisely state the objectives or purpose of this human specimen/data collection. State explicitly what diseases, conditions or processes will be studied.

This protocol seeks to build a pediatric Myelodysplastic Syndrome (MDS) and bone marrow failure disorder (BMFD) patient registry and tissue bank that will allow us to systematically evaluate patients with these rare disorders and gather sufficient patient material to permit systematical and in depth analysis in the future. We will also include myeloproliferative disorders (MPD), specifically myelofibrosis (MF) in our registry. The registry will collect relevant cinical data as well as a comprehensive tissue repository which will include peripheral blood (PB), bone marrow (BM) specimens, germ line tissue such as buccal mucosa swabs and potential other tissue biopsies for future research use. The ultimate goal is to define the genetics and underlying biology of childhood MDS and BMFD, identify pathways for therapy, and ultimately translate this knowledge to improve the outcome for these children.

The primary objectives of the study are:

1. To collect tissue and body fluid samples from children with known or suspected MDS or BMF.
2. To establish a uniform protocol for handling and collecting such tissue and body fluid samples and to have a uniform consent process and standardized plan for clinical follow up for those patients.
3. To maintain a comprehensive bank of well annotated tissue samples of cryopreserved cells, frozen tissue, and DNA from patients with MDS or BMF.
5. To provide tissue samples to researchers at Children's Hospital Boston, the Dana-Farber Cancer Institute and collaborators for investigations of MDS or BMF.

The secondary objectives are:

1. To improve the accuracy of the diagnosis for children and young adults with MDS and BMF disorders by a standardized review of morphology and standardized cytogenetics and molecular analysis.
2. To evaluate the frequency of the different subtypes of MDS and BMF disorders in children by using a standardized diagnostic approach.
3. To evaluate the frequency of cytogenetic and molecular abnormalities in MDS and BMF disorders.
4. To assess survival for children with MDS and BMF disorders.
5. To evaluate relapse rate, morbidity and mortality in children with MDS and BMF disorders treated with hematopoietic stem cell transplantation (HSCT).
6. To assess novel laboratory tests (e.g. as flow cytometry) in their utility as a diagnostic tools in the diagnosis of MDS and BMF disorders.

Justify why collection of these specimens/data are warranted scientifically. Summarize briefly the knowledge to date about the disorders, or conditions under study. Describe the general directions for the research. If the purpose of the storage is for undefined or general uses, please describe the types of research expected, providing examples.

Pediatric myelodysplastic syndrome (MDS) is rare hematopoietic disease in children. To date very little is known about the initiating events leading to the disease. The heterogeneity in the clinical and laboratory presentation has made it difficult to study the disease and to identify novel genetic alterations. Therefore no targeted therapies exist and a HSCT is the only therapeutic option for those patients.
In order to be able to study the disease systematically a large number of samples that are well annotated with a clinical history and ancillary information such as cytogenetics are needed. To date such a large sample collection does not exist within the USA. This protocol seeks to build a pediatric MDS patient registry and tissue bank that will allow us to gather sufficient patient material to permit systematical and in depth analysis in the future.

A repository of blood and bone marrow cells is a core resource for investigators of childhood hematologic disorders. Such a resource has the potential to play a significant role in the discovery of genes and cellular mechanisms involved in childhood blood disorders and may promote the identification of novel biologic predictors of outcome and development of targeted therapies. The primary goal of this protocol is to provide an organized and monitored process for collecting, processing, archiving, and distributing blood and bone marrow samples for use in research from patients with suspected or known myelodysplastic syndrome (MDS), acquired or inherited bone marrow failure (BMF) disorders, and myeloproliferative disorders (MPD). Furthermore clinical data will be collected from patients with MDS, BMF disorders and MPD. This will allow correlating biological variables with clinical data and outcome for translational research. Lastly we seek to evaluate the frequency of the various types of MDS, BMF disorders, and MPD by using standardized diagnostic approaches, including centralized review of the patients pathology at CHB. The blood and bone marrow samples collected for this tissue repository will be stored indefinitely until utilized for basic and translational research on MDS, BMF disorders, and MPD conducted by investigators at Children's Hospital Boston and their collaborators.

At the start of the registry we seek to explore the utility of flow cytometry analysis in the diagnositic work-up of patients with MDS. Pilot flow cytometry analysis will be carried out using multiple immunophenotypic surface markers panels to evalute defects in differentiation and maturation. If our pilot study will be successful we will conduct more extensive follow up studies thereafter.

On a subset of patients, we seek to obtain somatic cell samples from patients with known or suspected genetic disorders (in particular patients with MDS or MPD), for the purpose of creating pluripotent stem cell lines harboring disease-causing mutations. Such disease-specific induced pluripotent stem (iPS) cell lines will be invaluable tools for many basic and translational research applications, including pathophysiological studies in a developmental context, and

innovation and testing of genetic and cellular therapies. We will closely work with the laboratory of Dr. George Daley who already has a CHB IRB approved protocol (CHB protocol # 09-02-0068) using these techniques for patients with hematological conditions with an underlying genetic defect (such as inherited bone marrow failure disorders).

In the future we plan to utilize novel cutting edge technology such as high throughput whole genome wide screening approaches, high throughput genotyping to detect oncogenic mutations, high throughput sequencing to detect tumor suppressor mutations, and, potentially, deep sequencing to identify novel genes involved in pediatric MDS, BMF disorders, and MPD in the future.

10. PATIENT POPULATION: (describe patient population, i.e., diagnosis, age group, surgical/medical, etc. If applicable, provide an estimate on the number of subjects from whom data will be included in the repository/registry). The study will include patients with known or suspected MDS, known or suspected bone marrow failure disorders (inherited and acquired), and known or suspected MPD. All patients under the age of 35 years are elegible. The described disorders are rare and we anticipate enrollment of approximately 50-100 patients per year once we have initiated collaborations with other centers around the country. We expect that between 20-30 patients will be enrolled at CHB per year.

11. Complete these questions if this protocol includes the collection of biologic specimens for the establishment of a repository/registry (otherwise skip to question 12.)

A. Human biological specimens for this repository will be obtained from the following Children's Hospital sources Check all that apply:

- ☒ Clinical Labs
- ☒ Operating Room
- ☒ Inpatient Areas
- ☒ Outpatient Clinics
- ☒ Pathology
- ☐ Other procedure areas (endoscopy, urodynamics), specify
- ☒ Other sources or collaborators at outside institutions.

Please specify: We have initate collaborations with other centers around the country. Referring centers will obtain protocol approval through their own local IRB before enrolling patients. Individual patients cared for at other institutions may be consented over the phone by CHB accredited research staff of the MDS registry. This will be achieved with the assistance of their local health care provider.

B. Briefly describe the type of human material/tissue to be collected for this repository, e.g., blood, urine, tumor tissue, etc

Peripheral blood, bone marrow, material from buccal mucosa swabs or oral mucosa cell collection kits (Oragene collection kits) and skin biopsies will be collected. If a patient is undergoing additional tissue biopsies such as a lymph node resection or a tissue mass (chloroma etc.) that is part of their hematologic disease process and required for clinical care, we will also collect any excess tissue that is not needed for clinical diagnosis and is otherwie discarded.

For any of the specimens collected the patient can consent to none, some or all of the specimens collected for research use.

C. Human material/tissue collected for this repository will include the following. Check all that apply:

☒ Excess human material/tissue obtained for clinical care and determined to be in excess of that needed for clinical and diagnostic purposes (e.g., tumor that is leftover after pathologist's sampling has been completed).

Please explain where and how you will acquire the excess clinical specimens

Tissue will be collected from patients undergoing surgical procedures as part of routine clinical care (lymph node resection, chloroma, tumor mass). Fresh tissue will be submitted by the surgical team to the Pathology department. The pathologist and/or pathologist assistant will determine what tissue is needed for clinical care of the patient (excess/discarded tissue not needed for diagnosis). They will then determine what amount of tissue may be safely allocated for research use. Tissue will not be allocated for research without review of the pathology department. Once allocated, frozen specimens will be held and not used for studies until 2 weeks after the final diagnosis has been rendered. All other additional specimens may be utilized in study at the time they are allocated by the Pathology department as discarded/excess tissue for research. Specimens allocated by pathology staff for research use will be picked up directly by the PI (Dr. Hofmann) or the research teachnician and hand-delivered to the laboratory for further processing. Specimens collected will be tumor tissues and potentially surrounding non-tumor tissue (if applicable) resected as part of the surgical procedure. The tumor specimens will be collected from patients at the time of diagnosis, at recurrence, and during follow-up, but only if biopsies are performed for clinical purposes.

Blood and bone marrow specimens left over from previously performed procedures, if available, will also be utilized once it is determined by the clinical team and pathologist that those materials would be otherwise discarded and are not needed for diagnostic evaluation. One the primary care team (hematologist/oncologist or HSCT provider) and the pathologist determined that additional aspiration material, held in lab control for future use, is in access and not needed for diagnostic work up of the patient, the material will be picked up and hand-delivered to the repository by Dr. Hofmann or the associated research technician. In similar fashion the hematopathologist will determine if any access tissue from the bone marrow biopsy (typically histologic sections of paraffin embedded tissue) can be allocated for research use after the clinical diagnosis has been established.

☒ Prospectively collected human material/tissue obtained exclusively for research purposes during a clinically planned procedure, (e.g., cardiac biopsy at catheterization or open heart surgery, extra biopsies at endoscopy, additional intestine at gastric bypass, normal fat or skeletal muscle at surgery, extra CSF at LP, extra blood at phlebotomy)

Please explain where and how you will acquire the sample and how much extra will be obtained. Discuss any risks associated with specimen acquisition.

After obtaining informed consent, we will collect peripheral blood, and bone marrow samples from subjects. At all times these samples will be obtained at the same time that blood and bone marrow samples are obtained for clinical testing to avoid extra needle sticks and procedures. Patient blood and bone marrow samples will be obtained at diagnosis, after remission is achieved (if applicable), prior to HSCT and at the time of relapse (if applicable). If there are other diagnostic bone marrow examinations at other time points those materials will be handled in the same way. Blood and bone marrow specimens left over from previously performed procedures, if available, will also be utilized once it is determined by the clinical team and pathologist that those materials would be otherwise discarded and are not needed for diagnostic evaluation.

The following biological material will be retrieved from each patient:

A) Peripheral blood: up to 5 ml (1 tsp) for ages less than 2 years, up to 10 ml (2 tsp) for children 2-11 years old, and up to 20 ml (4 tsp) for children and adults 12 years or older of heparinized blood will be collected. Samples will be obtained during phlebotomy for a clinically indicated procedure whenever possible. Collection of these samples poses no additional physical risk to a subject when performed as part of clinically indicated phlebotomy, and the minimal risk limited to discomfort and bruising from venous puncture when performed for research purposes only. Samples up to 20 ml for any age patient that were obtained as part of a clinically indicated procedure and which are destined to be discarded will also be collected from the clinical laboratory.

Peripheral blood will be collected at the time of diagnosis, at the time of remission, prior to HSCT, and during the time of relapse (of applicable).

B) Bone marrow: up to 10 ml (2 tsp) of heparinized bone marrow will be collected. Samples up to 10 ml for any age patient that were obtained as part of a clinically indicated procedure and which are destined to be discarded will also be collected from the clinical laboratory.
For all patients of any age, samples will be obtained only during clinically indicated bone marrow aspiration by the practitioner performing the bone marrow aspiration. Collection of these samples poses no additional physical risk to a subject when performed as part of clinically indicated bone marrow aspiration.
The procedure may be performed as a bedside or office procedure under standard local anesthesia, under conscious sedation or general anesthesia as clinically indicated and determined by the primary care provider.
Post-procedure care for bone marrow aspiration will follow clinical standard of care guidelines.
Bone marrow specimens will be collected at the time of diagnosis, at the time of remission, prior to HSCT, and during the time of relapse (of applicable).

☒ Prospectively collected human material/tissue obtained exclusively for research purposes during a procedure performed solely for research (e.g., blood, urine, skin, muscle, saliva, breast milk, semen or cells from cheek swabs)

Please describe the procedure you will perform for research purposes to obtain the specimen. Include the size and quantity of the specimens and how often samples will be collected. Discuss any risks associated with specimen acquisition.

In addition to the specimens collected above, we will obtain germ line tissue from each patient as control tissue to the tumor tissue (such as blood, bone marrow or tumor mass biopsies). Possible germ line tissues include buccal mucosa cells and skin biopsies for skin fibroblast culture. In some instances the collection of buccal mucosa cells or skin biopsies might be indicated as part of their clinical care. In that case additional specimen will be collected for research purposes at the same time. If not already collected for clinical purposes we will consent the patient to collect the following material/tissue for research purposes only:

A) Oral mucosa cell collection/Buccal swabs: Buccal mucosa cells will be collected by using Oragen DNA self-collection kit available for infants, young chikdren and adults. Mucosa cells will be obtained by spitting into a collection container. Alternatively buccal swabs may be obtained by a study investigator by rubbing a cell collector such as the Cytobrush Plus across the buccal surface using standard procedures into tissue culture media. This is a non-invasive procedure, which poses minimal physical risk of transient discomfort to a subject of any age. This material will be collected at the time of diagnosis only.

B) Skin biopsy: Punch biopsies up to 2 mm for minors 0-17 years of age, and up to 3 mm for adults ages 18 years or older will be collected into tissue culture media. The procedure will be performed by a board-certified or board-eligible dermatologist, or a study investigator with privileges to perform skin biopsies at Children's Hospital Boston. In general, it is anticipated that most of the skin biopsy will be performed solely for research purposes. However, in most instances the study subjects will likley undergo sedation or anesthesia for any other procedures (such as a bone marrow aspirate and biopsy) efforts will be made to perform the skin biopsy at the same time to minimize pain and avoid additional anesthetics. In those cases we will perform the skin biopsy at the same insertion site as the bone marrow biopsy to avoid any extra minimal scar from the skin biopsy. In rare instances where this is not possible the punch biopsy will be obtained from a site on the upper extremity to be determined by the investigator performing the punch biopsy.
i. For patients 0-17 years old, the subject will be asked if there is a history of excessive scar formation, and if so, the subject will be excluded. EMLA will be applied prior to the procedure, followed by lidocaine/epinephrine local anesthesia. Subjects will be informed that collection of skin biopsy samples poses

the risks of pain and discomfort (similar to a blood draw), visible scarring at the biopsy site, and bleeding and infection at the biopsy site which will require keeping the area clean and covered with a Band-Aid for a longer period of time than a blood draw
ii. For patients 18 years and older, the skin biopsy may be performed as a bedside / office procedure under standard lidocaine/epinephrine local anesthesia. Collection of skin biopsy samples under these conditions poses physical risks of pain and discomfort during the procedure and of visible scarring at the biopsy site, and the minimal risks of bleeding and infection.

For skin biopsies of 2 mm, sutures will not be used. For skin biopsies of 3 mm, the wound will be closed with one 4-0 ethilon suture. All skin biopsy sites will be dressed with sterile white petroleum jelly and a Band-Aid. Wound care consisting of daily dressing changes will be explained to the subject. If a suture was placed, the subject will be instructed to have the suture removed by their primary care provider after 2 weeks. If there are any concerns or if the subject prefers for any reason, he/she will return to Children's Hospital to see the physician performing the biopsy at any time, and at 2 weeks for suture removal.

☒ Other sources or collaborators at outside institutions
Please describe how other sources will acquire the specimen and send them to you. Include whether the specimens are collected for your research only or whether the specimens exist for other purposes.

Once each collaboarting outside instituation has undergone their institutional IRB review for this study, they will obtain the same materials/tissues as outlined in section 11C. The materials will be shipped to the PI (Dr. Hofmann) research laboratory at CHB at no cost via overnight FedEx for immediate specimen processing.

D. Will immortalized lymphoblastoid cell lines, fibroblast cell lines or tumor cell lines be created from the collected human biological specimens? ☒ YES ☐ NO

E. Will you be performing any of the following with the samples?
- ☒ Biological assays
- ☒ DNA single gene studies
- ☒ SNP's
- ☒ GWAS
- ☒ Other, please specify

NOTE: Inexhaustible cell lines are considered of greater risk to confidentiality than finite samples that will eventually be entirely consumed by research

12. Complete these questions if this protocol includes the collection of data for the establishment of a registry/data repository.

A. SOURCE OF DATA: (check all that apply)

☒ Medical Record/Chart Review ☒ Electronic Medical Record ☐ Films/X-rays
☐ Quality Improvement Records ☐ Hospital administrative /billing records ☒ Other
Please specify: Clinical data provided by the primary clinical care provider on a study data froms (data collection froms)

B. What is the time period for the records that will be reviewed? (i.e. patient records from November 2000 to November 2010) From: **2009** To: **2034**

C. DATA TO BE COLLECTED

a. Check all that apply:

- ☒ Personal data (name, address, PCP)
- ☐ Billing data
- ☒ Demographic data (age, gender, vital status)
- ☐ Drug/device utilized
- ☒ Diagnosis
- ☒ Reports, clinic/office notes
- ☒ Procedures/treatment
- ☐ Location of Service
- ☒ Laboratory data
- ☒ Provider of Service
- ☐ Radiology Images
- ☐ Other, please specify: _____

b. Will any of the following health information/data be collected and stored in the repository/registry:

- ☒ HIV status
- ☐ Substance abuse (drug or alcohol abuse)
- ☐ Reproductive history (e.g., abortions)
- ☐ Other potentially stigmatizing concerns (psychiatric diagnosis)
- ☐ Sexual behavior/sexually transmitted disease.

NOTE: Attach data collection form(s), if forms have been developed.

13. RECRUITMENT & INCLUSION/ EXCLUSION

A. List inclusion and exclusion criteria for subjects (bulleted lists are preferred).No group of persons, for example, men, women, minorities, non English speaking should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Inclusion criteria
Patients have to meet one of the following criteria:

- **Suspected or known diagnosis of primary MDS (including familial MDS)**
- **Suspected or known diagnosis of secondary MDS**
  - **Secondary to bone marrow failure disorders**
  - **Secondary to chemo- or radiation therapy**
- **Suspected or known diagnosis of Myeloproliferative Disorders such as**
  - **Myelofibrosis (MF)**
  - **Essential Thrombocythemia (ET)**
  - **Polycythemia Vera (PV)**
- **Suspected or known diagnosis of Myelodysplastic (MDS)/Myeloproliferative Disorder (MPD)**
- **Suspected or known inherited bone marrow failure disorders such as**
  - **Fanconi Anemia (FA)**
  - **Dyskeratosis congenital (DC)**
  - **Severe Congenital Neutropenia (SCN)**
  - **Schwachman-Diamond Syndrome (SDS)**
  - **Diamond-Blackfan Anemia (DBA)**
  - **Bone marrow failure, NOS**
- **Acquired Severe Aplastic Anemia (SAA) or Very Severe Aplastic Anemia (VSAA)**

In addition the following two criteria need to be met:

- **Age less then 35 years**
- **Patient or legal guardian has given informed consent/assent. Consent will be obtained from the parents or legal guardian, or from patients over age 18 years. Assent will be obtained from patients as appropriate based on their developmental stage, but can be as early as 7 years of age.**

Exclusion Criteria

Patient will be inelegible if any of the following criteria are met:

- **Translocation characteristic of de novo AML like**
  - **t(8;21)(q22;q22) [AML1/ETO fusion gene]**
  - **t(15;17)(q22;q12) [PML/RAR α rearrangement]**
  - **inv(16)(p13q22) [CBFβ/MYH11 rearrangement]**
- **Myeloid leukemia of Down syndrome**
- **Known Acute Lymphoid or Myeloid Leukemia (NOT arising out of a background of MDS or BMF)**
- **Known Chronic Myeloid Leukemia (CML)**

Screening out:

Patients that have initially been evaluated as elegible patients based on a suspected diagnosis outlined in the elegebility criteria above, may later be found to have a diagnosis that is not compatible with the elegible diagnosis. Typically a confirmed diagnosis occurs after the initial clinical-histopathologic work up has been completed. Patients with acute leukemia (not arising out of a background of MDS or BMF), idiopathic thrombocytopenic purpura (ITP), autoimmune mediated cytopenias such as Evan's syndrome, or patients with infectious related cytopenias with out any evidence of an underlying MDS or BMF, will screen out once a diagnosis is established. Those patients will no longer be followed on study. Research materials that were already obtained will be saved and stored unless otherwise requested by the study subject.

B. Explain in detail the specific methodology that will be used to recruit subjects who will provide human biological specimens or have data abstracted from their medical records. Specify how potential subjects will *initially* learn about the possibility that specimens/data will be submitted to the repository/registry. Specify how, when, where, and by whom, subjects will be approached about providing samples or data? If recruitment is not applicable please explain why

Subjects will be identified and recruited using the following methods:

1) Local Recruitment: Potential subjects will be identified by the study investigators from the group of patients they encounter in the inpatient and outpatient practices of the Division of Hematology/Oncology. Patients will be approached during a care encounter (typically on the second or later encounter, and after the known or suspected genetic hematologic diagnosis emerges as part of their routine evaluation) to provide them with information on the study and to ask them to participate. The study investigator, research nurse or study coordinator will provide the patient with the Recruitment Letter (attached), a brief informative summary about the registry (attached), and a copy of the Consent Form (attached). The patient/parent will be given as much time as needed and encouraged to take consent forms home to go over the provided material and consent form and encouraged to ask questions or discuss the study with other members of the family. A follow-up meeting time will be arranged to answer questions, and sign consent. The biological specimen/s will be obtained as clinically indicated by the underlying disease process. Specimens will be obtained at the same time when the diagnostic procedure will be performed.

2) Local and Regional Recruitment: Local and Regional patient recruitment will come from our regional referral base. We already collaborate with those centers as they send us patients for second opinions, and referrals for HSCT. These centers include Massachusetts General Hospital, Boston, MA, Maine Children's Cancer Center Program, Dartmouth-Hitchcock Medical Center, NH, Albany Medical Center, NY, Baystate Health, Springfield, MA, Umass Medical Center, Worchester, MA, Hasbro Children's Hospital, Providence, RI, Connecticut Children's Medical Center, CT, and Yale, New-Haven, CT. We will continue to work closely with those local and regional pediatric centers to recruit patients. These institutions will recruit patients in accord with local IRB regulations. Patients will be recruited through their local primary Hematology/Oncology/HSCT providers. Primary hematology/oncology and hematopoietic stem cell transplant care providers (physicians, nurse practitioners and physician's assistants) at those institutions will be informed of the study by e-mail, letter (attached) or personal communication. The care provider will be asked to identify potential subjects for whom they provide care with known or suspected MDS or BMF disorders. Providers will be instructed not to perform patient database searches solely for the purpose of identifying potential subjects for this study. The study investigators will determine whether a potential subject identified in this manner is appropriate for the study. If the potential study subject is determined to be appropriate the research study coordinator, or research nurse will mail to appropriate potential subjects: (1) the Cover Letter from Primary Provider; (2) the Recruitment Letter, signed by both the PI Dr. Hofmann and the patient's primary hematology/oncology/hematopoietic stem cell transplant care provider; and (3) a copy of the Consent Form, indicating only the biological specimen(s) that are to be obtained and not the patient's diagnosis or clinical information.

If the patient is interested in participating in the study, the Recruitment Letters will instruct them to contact the Research Nurse. The Recruitment Letters will include an "opt-out" postcard (attached) for patients who are uninterested in the study and who do not wish to be contacted. If the opt-out postcard is not returned within 2 weeks, the Research Nurse or Research Coordinator will make one follow-up communication with the potential subject or subject's parents/guardian to see if he/she is interested in participating in the study.

Interested subjects will be screened for their eligibility in person or by phone. A follow up meeting time will be arranged by the Study Coordinator with the study investigator or Research Nurse to answer questions, obtain formal consent.

Drs. Inga Hofmann and David Williams will also be available by pager to answer any questions the subject may have.

3) National and International Recruitment: In the future we seek to expand our geographic referral base and working with additional institutions that we already have existing collaborations with and by networking with other centers around the country that have a particular interest in BMF disorders, MDS, and MPD. If individuals will be consented and specimens obtained at their local institution, each of those referring institutions will become a participating center in the registry with Children's Hospital remaining the primary coordinating study center. Each institution will obtain IRB approval from their local IRB. At that point the referring IRB approved sites will submit their notices of IRB approval to CHB IRB.

4) Innovative and alternative recruitment: In order to collect large numbers of patient samples in a rare disorder we need to investigate other arenas outside of local hospitals and clinics for identifying this patient population and recruiting them to minimal risk studies. Therefore we will use two additional tools to increase patient and physician awareness about the Pediatric MDS registry, which will include (1) a informative brochure for patients and providers, and (2) a patient and provider directed web site.

4a) Brochure: The brochure (attached) directed at patients will be posted in approved areas of the Children's Hospital and on our registry website. Patients and/or their legal guardians may contact Children's Hospital Boston of their own volition either via phone to the Coordinating study center (research nurse and study

coordinator) or via e-mail contact to the Pediatric MDS and BMF registry e-mail account (mds@childrens.harvard.edu). The Research Nurse (Grace Yoon) or Study Coordinator will send such self-referring individuals the Recruitment Letter (attached) along with a copy of the Consent Form. The mailing envolope will not contain any information that could suggest the patient's diagnosis or any clinical information.

4b) Web site: The use of the Internet to conduct clinical trials and as a tool for patient recruitment is a novel strategy that is currently underutilized. It has been shown to work well in previous studies carried out by other investigators at the Dana-Farber Cancer Institute (DFCI). The Internet provides a secure, confidential and convenient way to rapidly recruit patients for minimal risk studies. Using the Internet to recruit pediatric MDS and BMF patients will allow us to collect valuable information and patient research samples. In addition this will help us to explore how the Internet can facilitate clinical trials in a pediatric patient population.

We will advertise this study on the Children's Hospital Boston website (http://www.childrenshospital.org/pedimds) and the stand-alone website of the Pediatric MDS Registry and Bone Marrow Failure Disorder Patient Registry and Tissue Repository (http://www.PediMDS.org). We will also work with several non-profit patient organizations and the NIH to advertise our study through their websites and newsletters as well. These organizations include: MDS foundation (http://www.mds-foundation.org/), the NIH/NCI (http://www.marrowfailure.cancer.gov/), discussion forums for patients with bone marrow failure disorders (http://marrowforums.org/) and Aplastic Anemia MDS Foundation(http://aamds.org).
Members of the study team will not participate in web forum discussions to give medical advice or to survey forum discussant for active recruitment.

C. At the time of this submission will any "existing" (already collected) data/specimens be "grandfathered" into the repository/registry ☒ YES ☐ NO

If YES, describe the consent status of the specimens/data (what kind, if any, of consent was obtained for collecting the specimens/data?)
We will contact patients with known MDS or BMF through their primary care provider at CHB. We will ask if they are interested in participating in the registry even if treatment has already been initiated at the point of entry into the registry. We will obtain a separate informed consent from potential subjects to be able to retroactively collect medical information from their medical records and any potential remaining tissue that is not needed for clinical purposes.

Please include with this submission any consent document that may have been previously used to obtain these samples.

D. Will the subjects receive any remuneration? ☒ YES ☐ NO
IF YES, please describe.
Study subjects will be reimbursed for parking expenses for their visits to Children's Hospital Boston during which they participate in this study.

14. OPERATING POLICIES AND PROCEDURES OF THE REPOSITORY/REGISTRY

A. Duration of storage, labeling/coding, security of specimens/data: State how long you expect to maintain the repository/registry. Describe the acquisition, logging in, and tracking of specimens/data. Typically specimens/data are coded with a unique, random, identifying number in order to protect the confidentiality of research subjects. Explicitly state whether specimens/data will retain a key to the code linking the specimens/data to the individual from whom the specimen/data was obtained. Describe where the key to this code is kept and who has access to it. If, after obtaining specimens/data for a specific research goal, you plan to de-identify the remaining excess specimens/data for further research, clarify how and when this occurs.

The repository and registry will be maintained indefinitely. Study subject data collected by the primary care provider (hematologist/oncologist or HSCT provider) will be provided by filling out a standardized case report forms which are provided by the study center. The research nurse and/or study coordinator will confirm that data forms are filled out correctly, and assist providers with potential questions regarding the data from. Once the registration and data forms are received by the study center the nurse or study coordinator will the patient data from all identifiers and de-identify the patient with a unique de-identified code number. Data will be entered in to the research database by using the code number only. The code number consists of a nine-digit number as outlined:
CCCC – N N NN - X
CCCC= collaborating study center code
NNN=consecutive included patients. The patient number will continue successively in each state/country.
X= additional check code to improve quality assurance, i.e. the code number for the first subject from CHB will look like MA01-0001-X

Data will be captured on a unique database built by the Clinical Research Program (CRP) at CHB. Research samples collected for the tissue repository will be de-identified with the same unique de-identified code that will be used to capture patient data in the database. Sample tracking will be performed using the unique code number only through iLAB technologies systems. The specimen tracking technolgy (iLAB technologies) will also assign each sample an additonal unique bar code number.

Patient-derived material will be linked to patient clinical information using a unique numerical identifier. Any material or clinical data shared with collaborators, inside or outside of the participating institutions, will be supplied with the unique identifier numbers only, and without patient name, social security number, or other patient identifiers. The coding information (key) that links the patients information to the patient's clinical data and patient-derived material will be held in locked file cabinets and on passowrd protocted computers allowing very restricted access by the study investigators and study coordinator only.

For electronic information, describe how electronic security is maintained, including what password protections and virus software are enabled. Include whether you will follow the Children's Hospital security standards regarding laptops, encryption, web procedures, use of PDA's etc. Also describe how the system will be audited.

The electronic database and the electronic specimen tracking system will be maintained on passowrd protected CHB computers behind the CHB firewall system. The systems will be backed up through CHB IT services. All systems follow CHB security standards.

For paper-based information, describe where the identifiable information will be stored, who has access to the storage area, and how that access will be audited. If the information is stored off-site, describe how security at the facility is maintained and whether or not a business associate agreement has been or will be signed

Any paper based documentation (case report froms and key to unique identifier) will be kept in locked file cabines and in locked offices of the principal investigator and the research nurse and study coordinator only. No information will be stored off-site.

B. Processes for distribution of specimens/data: Clarify the process by which other investigators may request specimens/data from the repository/registry, if proposed. Describe who oversees the requests (e.g., an individual, group of individuals, or board), provide their qualifications, and describe the process for determining the merits or acceptability of the request for specimens/data. Specify which members of the repository staff (include roles and responsibilities) will have access to the identifying information. Describe what data/specimens are provided to requesting researchers, and what health/medical information will be distributed by the repository/registry. Note that any release of *directly identifiable specimens or directly*

identifiable health information, or a key to the code linking the specimen/data directly to an individual requires a separate, IRB-approved protocol Clarify who at the repository will assess specimen/data requests and ensure that, where necessary, there is a current IRB-approved protocol covering the proposed research.

Research data collected or maintained by the NIH-funded Pediatric MDS and BMF disorder registry at CHB will be made available as shared data for research purposes. Investigators inside and outside CHB may request specimens and data from the repository and registry.

Each investigator must go through a formal review process to obtain samples from the repository by submitting a formal written request including a brief research proposal to the steering committee of the Pediatric MDS and BMFD reigistry and tissue bank. The research data and sample request will be reviewed by the Steering Committee of the Pediatric MDS and BMF disorder registry. Investigators participating in the registry will have preferred rights to any outside investigators.
Steering Committee composed of the following members:

- **David A. Williams, MD (Pediatric Hematology/Oncology)**
- **Mark D. Fleming, DPhil, MD (Pediatric Hematopathology)**
- **Inga Hofmann, MD (Pediatric Hematology/Oncology and Hematopathology)**
- **Kevin Shannon, MD (external advisor-University of California San Francisco)**
- **Charlotte Niemeyer, MD (external advisor-Albert-Ludwigs University Freiburg, Germany)**
- **William Woods, MD (external advisor-Children's Healthcare of Atlanta at Egleston, Emory University School of Medicine)**

Patient-derived material will be linked to patient clinical information using a unique numerical identifier. Any material or clinical data shared with collaborators, inside or outside of the participating institutions, will be supplied with the unique identifier numbers only, and without patient name, social security number, or other patient identifiers. The coding information (key) that links the patients information to the patient's clinical data and patient-derived material will be held in locked file cabinets and on password protected computers allowing very restricted access by the study investigator (Dr. Hofmann), supervising associates (Dr. David Williams, Division of Hematology/Oncology, and Dr. Mark Fleming, Department of Pathology, both PI on the NIH funded grant) and study coordinator and research nurse (Grace Yoon, RN, NNP) only. Outside investigators or collaborators will not have access to the coding information key. Research data captured in the database will be stored securely on password-protected computers. Access to the database will only be granted to the investigator and research staff. Only limited demographic information (age in years and gender) and non-identifying medical information (diagnosis and clinical/laboratory parameters) will be provided to the laboratory investigators.

C. Distribution of specimens/data that is coded, but not directly identifiable, when the recipient researcher will not seek to identify the individual from whom the specimens were obtained, is not considered *human subjects research*. However the recipient researcher must agree in writing to never attempt to access identifiable health/medical information or to attempt to identify the subject(s) who provided the specimen/data. Such coded specimens/data may be distributed *without separate, independent* IRB approval once the recipient researcher signs the agreement stating that s/he will not attempt to identify human subjects from whom the specimens/data were derived. Provide a copy of a formal letter or form that recipient investigators will be asked to sign for such distributions.

Please include a copy of any letter or agreement recipient investigators will be asked to sign.

D. Re-contact of subjects providing specimens/ data to a repository/ registry: In general, investigators are advised to plan ahead carefully and describe potential uses and sharing of repository/registry materials, so that approved research that subjects have agreed to may proceed without the need to re-contact subjects. Re-contact of subjects to obtain consent for new types of research, collect additional samples, or provide clinically relevant information may be required in some situations and may require separate IRB approval if not fully defined at the time of repository inception.. Research results may not be clinically useful or validated, and may not be ready for return to patients or physicians. If it is anticipated that subjects will be re-contacted by representatives of the repository/registry, please describe in detail: (1) reasons for re-contact; (2) how and when re-contact would occur, or might occur, if not obligatory; (3) how subjects will provide updated contact information, if necessary; (4) whether the consent provides an option for "no re-contact" if this is possible and reasonable; (5) what research information would be released to subjects or placed in medical records; (6) what counseling would be provided, and what notification of subject's physicians would be undertaken, if any.

1) We are not anticipating the need to recontact individual study subjects in the future beyond the study participation and data collection they have initially consented for. For those planned routine follow up visits (as outlined in consent from) study subjects will be contacted by their primary care provider at pre-determined time intervals (every 6-12 months), which will be part of their routine clinical care. At those time points cinical data and possible research specimens (if applicable) will be collected. Clinical data will be recored by the primary care provider on case report froms. Study sujects are not scheduled to be contacted by study staff directly after initial registration.

2) In case of new research developments such as follow up research studies resulting from this registry we might re-contacting study subjects in the future after obtaining additional IRB approval if indicated. If possible we will do so through or with permission of their primary care provider. We will inform patients of this possibility in the consent of the original study and provide the patient with the option to op-in our opt-out of being recontacted in the consent from.

3) Study subject contact information will be kept up to date through the primary care provider. In addition study subjects will have the option to update their contact information at the coordinating study center.

4) The consent will provide a option for "no re-contact" (see consent from).

5) An additional copy of the research consent will be stored in the CHB medical records. This allows other medical providers of the hematology division and their associate staff to access the consent and confirm the study subjects participation in this study. This will avoid confusion and errors in the case that additional research samples will be obtained at the same time when routine clinical diagnositic tests will be performed such as blood draws and bone marrow aspirates. Reseach data will NOT be stored in the medical records with the excetipion if a research laboratory test becomes a CLIA certified clincal test that will impact or change clinical care of the patient. Specific research information will not be released to the study subjects.

6) There is potential for emotional and psychological discomfort for individuals participating in any research study and donating cells or tissue samples to be used for research. The Consent From outlines that the aim for the Pediatric MDS and BMF patient registry and tissue repository serves the main purpose of understanding the underlying disease biology of those disorders. Genetic research performed on patient samples will only be carried out to understand the biology of MDS and BMF. The Consent Form states that patients uncomfortable with the thought of their cells, tissue or clinical data being used for research purposes should not participate in the study.

E. Clarify with whom specimens /data will be shared. Possible options include: (a) only within Children's; (b) only with academic collaborators; (c) with academic and commercial (for-profit) collaborators. If specimens/data will be shared with collaborators at for-profit companies, please state this explicitly.

Research data and specimens will only be shared with study collaborators within CHB and potentially with outside academic collaborators after they have undergone a formal review process through the streering committee as outlined in section 14B above. Data will NOT be shared with for-profit or commercial institutions.

The provision of human biological specimens to academic collaborators requires an academic Uniform Biological Materials Transfer Agreement (UBMTA), available from the Clinical Trials Office. Children's Hospital also recommends that you consider using a simple, faculty-approved collaboration agreement [LINK] which is designed to fairly address publication, data access and similar issues. Some departments may also have department-specific applications or agreements to access or share specimens
The provision of human biological specimens to for-profit collaborators requires the existence of a bona fide intellectual collaboration between the Children's Hospital investigator and an individual or group at the for-profit site, and a Materials Transfer Agreement (MTA) executed by Children's Hospital. Please contact the Clinical Trials Office for assistance with these agreements

15. RISKS

Risks to privacy and confidentiality should be discussed below. Clarify in this section any medical risks to subjects (e.g., risks of phlebotomy, or bleeding, infection, or scarring as a result of a biopsy performed solely for research purposes). Although uncommonly undertaken, if health/medical information from the research is returned to subjects or their physicians, discuss the potential risks, such as anxiety, or of false positive or false negative results.

All blood, bone marrow and other tissue samples will be obtained at the same time that procedures are being performed for clinical purposes. Therefore, there is no incremental risk of participating in the study beyond the risks that may occur with routine blood draws, bone marrow aspiration and biopsies. Specifically those risks are:

A) Acquisition of buccal swabs poses only minimal risk of discomfort at the moment of sampling.
B) Acquisition of peripheral blood or liquid bone marrow specimen obtained during medically indicated procedures and (1) destined to be discarded, or (2) taken as additional samples for research purposes in the quantities specified above, poses no risk beyond that of the specific procedure itself.
C) Acquisition of peripheral blood by phlebotomy solely for research purposes poses the minimal risks of pain and bruising from venipuncture.
D) Acquisition of bone marrow solely for research purposes in subjects greater than 18 years of age poses risks of pain, bleeding and infection.
E) Acquisition of skin biopsies solely for research purposes poses the physical risks of pain, bleeding, infection and visible scarring.
F) Provision of medical and demographic information as specified above poses the risks of invasion of privacy and loss of confidentiality. These risks will be discussed in the Consent Form and minimized as discussed in section 18.
G) There is potential for emotional and psychological discomfort for individuals donating cells for future research. The Consent Form states that patients uncomfortable with the thought of their cells being used for research purposes should not participate in the study.

H) Though the tissue sample provided to the researchers will be stripped of patient identifiers, the genetic content of the cells obtained could theoretically be used (albeit with enormous difficulty) to identify the donor. This risk is discussed in the Consent Form.

Skin biopsies obtained solely for research purposes in minors (E, above) will be considered minimal risk as defined by the Institutional Review Board as they meet the following stipulations: limited to 2 mm in diameter and not requiring sutures; EMLA anesthetic will be applied prior to the procedure; minors who have a history of excessive scar formation will be excluded from providing a skin sample for the study; the subjected will be consented to the likelihood of discomfort similar to a blood draw, but that the wound site will require cleaning and coverage for a longer period of time than a blood draw.

16. BENEFITS

It is not expected that subjects providing specimens for repositories will derive personal health benefits as a result of their contributions to specimen repositories. However, explain any specific future benefits that might be expected to accrue to individuals, families or groups of affected individuals. Indicate what medical, scientific, and societal benefits are likely to accrue as a result of research performed on specimens in this repository.

In most instances there will be no direct benefit to the patients who participate in this study. Detection of genetic alterations causing MDS or bone marrow failure disorders may provide future benefits to patients. This will not be a direct benefit, as we will require repeat blood draw and certification of the results by the clinical lab for reporting to families.
Increased knowledge about disease states may lead to future diagnostic tests or treatments of direct benefit.
Prognostication-patients found to have known (reported) mutations with established natural history may be counseled about their prognosis, once the results are replicated by the clinical lab. As more knowledge is gained about the specific mutations and the clinical course for patients, this type of better prognostication will be possible for more patients.

17. PROCESS TO ADDRESS UNINTENDED CONSEQUENCES. EVENTS, RISKS.

Describe who reviews and analyzes reports of any adverse events, breaches of confidentiality or complaints and forwards them to the IRB, and how and when these events are reported to the IRB. Describe how unanticipated problems involving risks to subjects or others (e.g., staff, families of subjects etc) will be reported to the IRB. Comment on whether any other regulatory bodies (e.g., FDA, NIH, or other IRBs) will also receive reports or such events, if this is relevant.

Protocol violations and unanticipated problems involving risks to research subjects and others including adverse events will be reported as mandated by the CCI guidelines.
Though all precautions will be taken to avoid complications resulting from specimen collection, excessive bleeding, infection, excessive visible scarring and other complications could occur from bone marrow aspiration or skin biopsy. Subjects will be instructed to monitor for these signs and symptoms. If they occur, the study investigator or physician performing the procedure is to be contacted. Any such complications will be reported as an adverse event.

18. HIPAA/Privacy/Confidentiality.

A. Describe methods used to protect the privacy of subjects and maintain confidentiality. Clarify whether special attention to confidentiality is necessary because of the nature of the research (i.e., the research involves collection of particularly sensitive personal information, for example, HIV status, reproductive history, data on illegal activities or drug use, or other potentially stigmatizing behaviors). Comment on whether a Certificate of Confidentiality has been obtained, if relevant. Specifically address where individually identifiable information will be stored and who will have access to such data. Explain how the potential for breaches of confidentiality and resultant risks to dignity, insurability and employment are minimized. Because genetic data may affect not only the individuals providing samples, but also their family members, or social groups, comment on potential psychosocial risks of genetic studies or DNA repositories to these extended groups also.

Privacy Provisions

Privacy will be protected during recruitment in that potential subjects will be recruited by a practitioner known to them or with the endorsement of a practitioner known to them (e.g. co-signature on recruitment letter). Database searches will not be conducted for the purpose of identifying potential subjects. Privacy will also be maintained by omitting reference to the subject's diagnosis in the Recruitment Letter and copies of Consent Forms mailed to their homes. Settings for discussions of the research protocol and acquisition of consent and medical/demographic information will be limited to (1) phone calls with the subject himself/herself or the subject's legal guardian/custodian (where applicable) from appropriately private locations (e.g. medical staff office, practitioner's office or physician workroom); (2) face-to-face conversations with the subject himself/herself or the subject's legal guardian/custodian (where applicable) in appropriately private locations (e.g. practitioner's office or clinic exam room).

Confidentiality Provisions

Patient-derived material will be linked to patient clinical information using a unique numerical identifier. Any material or clinical data shared with collaborators, inside or outside of the participating institutions, will be supplied with the unique identifier numbers only, and without patient name, social security number, or other patient identifiers. The coding information (key) that links the patients information to the patient's clinical data and patient-derived material will be held in locked file cabinets allowing very restricted access by the study investigators and study coordinator only. Research data captured in the database will be stored securely on password-protected computers. Access to the database will only be granted to the investigator and research staff. Only limited demographic information (age in years and gender) and non-identifying medical information (diagnosis and clinical/laboratory parameters) agreed upon in the Consent Form will be provided to the laboratory investigators.

Check below any of the following identifiers that will be recorded with or linked by code to the data:
Data that are coded, where the key to the code is accessible to researchers, are considered protected health information (PHI) subject to HIPAA regulations.

x☐ Name	**x**☐ Electronic email address	☐ Medical device identifiers and serial numbers
☐ Social security number	☐ Web URLs	☐ Biometric identifiers (finger and voice prints)
x☐ Medical record number	☐ Internet protocol (IP) address	☐ Full face photographic image
x☐ Address by street location	☐ Health plan beneficiary number	☐ Any other identifier or combination of identifiers likely to identify the subject
x☐ Address by town/city/zip code	☐ Account number	
x☐ Dates (except year), e.g., date of birth; admission/discharge date; date of procedure; date of death	☐ Certificate/license number	
	☐ Vehicle Identification number and serial number, including license plate number	
x☐ Telephone number		
☐ Fax number		

19. INFORMED CONSENT AND AUTHORIZATION

A. Will informed consent be obtained for data/specimen collection and storage? x☐ YES ☐ NO

If YES:

A. Explain in detail how, where, and by whom informed consent will be obtained from the subject providing specimens/data. Describe timing of consent, including how long subjects will be given to consider participation. Describe the qualifications and experience of the individuals who will be obtaining consent (e.g., genetic counselor, licensed physician, nurse practitioner). Describe how the principal investigator will be available for consultation or questions, when informed consent is obtained by someone other than the principal investigator.
Please refer to Form Part C:Consent, Assent &HIPPA info form, Section 1, questions 1-5 for a detailed description about the consent process.

B. When applicable, explain how provision of specimens/data to more than one repository is discussed with subjects. Typically each repository has a specific consent form.
N/A

C. What will happen when subjects turn 18? If this is a repository that continues to collect specimens or data from medical records on an ongoing basis, if the parents provide initial consent for a child, what steps will be taken when the child turns 18 to get their consent for continued collection or when a child becomes capable of assent? If this is a long term collection, what process will be used for obtaining ongoing consent/assent? If this is a one time collection from children less than 18 an/or it will be impracticable to contact subjects when they turn 18 (i.e. not able to locate patient , no longer a patient, have not maintained contact) Please complete the waiver questions E-H so a waiver can be applied when subjects turn 18.

Once the tudy subject/patient turns 18 study staff will approach the patient to get their consent for continued collection of follow up data or research specimens (were applicable).

D. If Children's investigators will not be obtaining informed consent from all subjects, but others collaborators will obtain consent, (perhaps even from outside institutions) clarify how the collaborators will provide you with documentation of consent and IRB approval of the relevant protocol and consent forms.

CHB investigators and all future participating institutions will obtain consent from each study subject prior to entry in the study. Referring institutions will provide the coordinating study center at CHB with a copy of the informed consent/assent before the patient will get enrolled in the study. Patients without

consent will not be enrolled in the study, data will not be entered into the database and specimens will not be collected and stored. Participating institution must go through their local IRB approval process.

If NO:

If informed consent will not be obtained for the collection and storage of human biological specimens in the repository, address each of the following regulatory requirements to obtain a waiver of informed consent.

E. Explain why the research could not practicably be conducted without access to and use of the identifiable health information/data

N/A- all health information and data will be de-identified.

F. Explain why the research involves no more than minimal risk to subjects. Specifically explain why the research involves no more than minimal risk to the privacy of the individuals

Research specimens and data have been de-identified using a numerical code. Therefore the information cannot be linked to the study subject. Only the PI of the study and restricted study staff have access to the code, which is kept in locked file cabinets in locked offices and on password protected computers. Therefore ongoing participation of an individual that turns 18 and cannot be re-consented directly will only pose minimal risk to the subject in regards to privacy.

G. Explain why the waiver of consent/authorization will not adversely affect the rights and welfare of the individuals

A waiver of consent will only take place once a study subject turns 18 and a re-consent process for prevoiously collected specimens and data cannot be obtained because the patient is deceased or lost follow up. In this case specimens have already been obtained and therefore do not affect the physical walfare of the study subject. Research data remain de-identified as outlined in question F above.

H. Explain why the research could not practicably be conducted* without the waiver of informed consent and authorization

Reasons for waiver of informed consent and authorization will most likely apply to individuals when they turn 18 years of age and cannot provide a re-consent for the following reasons: 1) loss of follow up, 2) contact information not current/not upated, 3) patient deceased. Given that the overall number of study subjects in this registry will be small it will be difficult to conduct a statistically powerful research analysis if a waiver of consent cannot be applied in the specific scenerios described.

Please Note for 19.H. you need to explain **why the research could not be conducted if informed consent is required. It is not enough to explain that there are insufficient resources or time available. Common reasons include, patients are lost to follow-up, may have been seen years ago so there is not current contact information, patients may be deceased, etc. If all the subjects are currently seeking care at the hospital it would be possible to ask for their consent to review their record for research purposes and it may not be possible to satisfy this criterion.*

20. WRITTEN ASSURANCE AND SIGNATURE

My signature below provides written assurance that identifiable information will not be reused or disclosed except as required by law; for authorized oversight of research; or for other research only if that research has been reviewed and approved by the IRB with specific attention to and approval of the issue of access to this identifiable information.

Signature of PI _____ Date _____

21. DEPARTMENT/DIVISION SIGNATURE

This protocol has been approved for submission to the Committee on Clinical Investigation. The PI and staff have:

1. the appropriate resources (equipment, space, support services) to perform the research.
2. the time necessary to oversee the conduct of the research.
3. the appropriate qualifications, training, credentials/licensure to perform the associated research procedures.

I have reviewed and approved the investigator's plans for covering the expenses associated with providing medical care in the event of a research related adverse incident.

Signature of Department Chair, or Division Chief (if PI is in Dept. of Medicine) _____ Date _____

- If PI is a Department Chair, signature of Carleen Brunelli, PhD is required

***NOTE**: Investigators requesting data from the repository or database for individual projects with identifiers should submit a separate application for IRB review and approval*