

Recommendations From the International Stroke Genetics Consortium, Part 2

Biological Sample Collection and Storage

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The revolution in human genetics, catalyzed by the sequencing of the human genome in 2003 and the development of genome-wide genotyping technologies, has led to the identification of >2000 trait-associated genetic variants. Because most of these variants have individually small effects on disease risk, successful gene discovery efforts have required large sample sizes (involving thousands, tens, or hundreds of thousands of cases and controls) to achieve sufficient study power. Amassing such sample sizes has depended on international collaboration on a scale never seen before in human genetics or even in clinical research. Disease-specific consortia bringing together many individual sites and collaborators have now evolved for many major diseases. Each

consortium has faced with ≥ 2 fundamental questions: how to assemble a study sample of sufficient size, homogeneity, and phenotypic quality and how to retain and analyze, sometimes repeatedly over several years, biological samples from enrolled subjects.

The International Stroke Genetics Consortium Biorepository

The International Stroke Genetics Consortium (ISGC) has addressed these 2 challenges by taking into account the nature of the disease—stroke occurs suddenly with high case fatality (≤ 251 per 100 000; 5.9 million of 53 million reported deaths in 2010)^{1,2} and develops through multiple biological

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mechanisms. Because the stroke community consists of clinicians and investigators from across the world practicing in a range of environments with varied resources and constraints, the ISGC has developed processes that allow maximum flexibility while maintaining standardization, reliability, and quality. A central tenet of the consortium involves transparency and trust, without which large-scale collections and studies would not be possible. The growing collection of stroke samples created at the Massachusetts General Hospital under the auspices of the ISGC includes physical samples for ≈5000 cases and 4500 controls from >20 institutions in Europe, North America, South America, Australia, and Asia. It provides a state-of-the-science biorepository that ensures reliable stroke clinical data and samples are available for use in future research.

Here, we outline the processes and infrastructure necessary for individual sites to collect and contribute samples to large-scale genetic efforts. Throughout this article, a central site refers to the coordinating site that houses the samples and data contained within a biorepository, whereas a contributing site is defined as a site that enrolls research subjects, collects samples and data, and sends samples to a central biorepository. Our companion article describes standardized phenotypic data collection, population selection, demographic information, stroke subtyping, neuroimaging standards, outcome definitions, and pertinent ethical considerations.^{2a}

Biorepository Models

Several approaches are available to establish a biorepository for large-scale collaborative genetic studies, each with specific advantages and challenges. A genetic biorepository includes physical samples, genotyping data, or both, for a large set of individuals with a phenotype of interest, along with control subjects.

Electronic Medical Record Data With Associated Sample Collections

This approach is cost-effective because it uses data already collected for routine purposes (eg, billing) and discarded clinical samples for genetic analysis. Challenges include local ethical and institutional limitations, as well as a need for a high-quality electronic medical record system and carefully constructed algorithms to characterize phenotypes of interest properly. The Vanderbilt University-led BioVU³ and National Human Genome Research Institute-funded Electronic Medical Records and Genomics (eMERGE)⁴ network are primary examples of this sort of collection, organized by the National Human Genome Research Institute to combine DNA biobanking with electronic medical record-based phenotyping.

Assembly of a Biorepository From Existing Research Collections

This approach involves centrally assembling samples already collected elsewhere before the collaboration. The primary advantage of this approach is its low cost because it takes advantage of existing collections not originally assembled

expressly for genetic studies, using samples from which DNA can be extracted. Challenges include the inability to modify sample or data collection and handling at local sites, and ethical considerations when data and samples were collected some time ago and new uses may be different from those originally approved by local ethics committees. Studies that have used this strategy are the ISGC-Wellcome Trust Case Control Consortium 2 Genome-Wide Association Study,⁵ the National Institute of Neurological Disorders Ischemic Stroke Genetics Network,⁶ and the ISGC's genome-wide association study of intracerebral hemorrhage.⁷

Centrally Coordinated Prospective Study

Advantages of this approach include central control over the entire process, resulting in the least possible heterogeneity in quality control, data, and samples. The major challenge to this approach is its high-cost. Nested case-control studies constitute an appealing strategy to keep the advantages of a cohort design, while reducing costs. This design entails ascertaining 1 or several outcomes over time in a complete cohort, with ascertainment of exposure (genotypes in this case) in a given number of controls each time a case occurs, minimizing genotyping costs. Another drawback for this approach is the time necessary for incident cases to accumulate. For example, with 500 000 participants, the UK Biobank⁸ had 7000 prevalent strokes at the baseline, presently has 3000 participants with stroke, and expects 20 000 stroke cases by 2027.

Data Sharing

Retaining genotyping data allows subjects to be included in future analyses. In silico data are, thus, often transferred from a repository for multiple different collaborative studies, provided each study falls within the scope of the permissions granted for use of the samples. In silico sharing of genetic data can involve either summary statistics or individual-level genotype data. Sharing of summary statistics is easier, and approval from human studies committees is generally faster to obtain than approvals required for the sharing of individual-level data. However, the precision and sophistication of analyses that can be completed using summary statistics are limited compared with what can be achieved with pooled individual-level data. The ISGC's METASTROKE collaboration^{9–11} has used pooled summary statistics to great effect. Through the sharing of individual-level data, however, the Psychiatric Genomics Consortium^{12,13} has made far more substantial advances.

Essential Biorepository Components

Study Protocol and Regulatory Approvals

Before participating in a central biorepository, contributing sites must confirm that they comply with regulatory approvals required by their home institutions and documentation required by the central site. Requirements vary widely by country and individual institution. Although many regulatory approvals are relevant to a biorepository protocol, the most important describes the sharing of samples and data

to outside institutions; specifically, to the central site of the biorepository.

If the contributing site's consent form does not clearly address sample and data sharing, documentation of a regulatory amendment granting approval may need to be sent to the central site. Because sharing among all biorepository contributors will allow for greater scientific discovery, the contributing site should also consider amending its protocol to allow samples and data to be sent to and analyzed by any member of a given consortium.

Although the above recommendations are based on the ISGC experience at Massachusetts General Hospital, other institutions cite different experiences, when seeking approval for sample sharing (Table). Although each site may differ, certain requirements are common to all institutions. First, some type of approval must be granted before transfer. These include either review of the study protocol or research proposal by the contributing institution's ethics committee, or the completion of a material transfer agreement or institution-specific transfer certificate. Second, shared samples and data must be often de-identified. Less widespread requirements include registration of transferred samples with the Department of Health (Taiwan) and the reconsent of subjects, when the research proposal differs from the original consent (Utah). Finally, a requirement specific to all National Institutes of Health (NIH)-funded sites includes certification that the submission of all NIH-funded data to the database for Genotypes and Phenotypes NIH repository and subsequent sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained. Sites anticipating NIH funding must complete a verification letter, signed by both the regulatory committee Chair and the principal study investigator and certified by the responsible Institutional Official before sending any samples or data to the biorepository. An overview of current NIH policies on data sharing in genome-wide association studies can be found on the NIH Web site, including links

to a draft NIH genomic data sharing policy.^{14,15} An overview of database for Genotypes and Phenotypes policies can be found on the database for Genotypes and Phenotypes Web site.¹⁶

Because of the variety of required approvals, we recommend that any site expecting to share samples outside of its home institution includes language on sample sharing in its regulatory protocols and consents as early in the study as possible. In addition, study investigators should review institution-specific requirements to ensure that these approvals are met. It is important that an ongoing dialogue exists between contributing sites and the central biorepository as requirements may change over time and protocol or sample use modifications may be necessary.¹⁷ Sample informed consent and protocol summary forms are provided (Figures I and II in the online-only Data Supplement).

Uniform Phenotype Data Collection

When enrolling subjects or collecting samples for analysis, it is important to collect certain items from an agreed minimum phenotype data set, allowing coding to a standardized format, so that samples from different institutions can be used harmoniously within a biorepository. This avoids haphazard, nonuniform collection by creating a standardized minimum data set with additional optional layers of details available. To prevent the need for interpretation and data cleaning at the central biorepository, a common variable and coding definition sheet may always be referenced, when reporting/sharing data. ISGC recommendations for accurate, clear, and uniform phenotyping protocols are described in the companion ISGC article.^{2a}

Standardized Sample Collection and Processing

We recommend that all sites follow a standardized sample collection and processing procedure. This helps to guarantee that collected samples are of high-quality and will be useful

Table. Survey of Ethics Committee Requirements for Sample Sharing With a Central Biorepository for 11 Institutions From Around the World

Region	Country	Institution	Able to Share Samples	Requirements		
				Approval by IRB or Review Committee	Sharing Statement in Protocol	MTA or Transfer Certificate
North America	NC, US	Duke University	Yes	X	X	X
North America	UT, US	University of Utah	Yes	X	X	X
Europe	Belgium	University Hospitals Leuven	Yes	X
Europe	Finland	Helsinki University Central Hospital	Yes	X	X	...
Europe	Spain	Hospital del Mar, Barcelona	Yes	X	X	X
Europe	Sweden	Lund University	Yes	X	X	X
Africa	Malawi	University of Malawi	Yes	X	X	X
Asia	Korea	Centers for Disease Control and Prevention	Yes	X	X	X
Asia	Singapore	National Neuroscience Institute	Yes	X
Asia	Taiwan	Chang Gung University	Yes*	X	...	X
Australia	Australia	University of Newcastle	Yes	X	X	...

IRB indicates institutional review board; MTA, material transfer agreement; NC, North Carolina; US, United States; and UT, Utah.

*Governmental permission required to share samples.

in future experiments. Samples can be shipped as either whole blood or extracted DNA.

The DNA concentration of each sample may vary based on several factors, including time to initial processing, white blood cell concentration, and volume of the blood draw. It is important to have a reliable value for DNA concentration of a sample to assess its viability for inclusion in genetic studies. Contributing sites with the resources to extract DNA should agree on a standard procedure with the central site, including the specific extraction kit, desired sample concentration and volume, quality control measures that will be conducted by the contributing and central sites, the frequency of shipments, and the format for sample shipment.

Implementation of protocols for sample collection and processing has helped facilitate a streamlined workflow between contributing and central sites for the ISGC, while increasing efficiency as the size of the biorepository has expanded. Protocols describe DNA extraction, DNA quantification, DNA storage and sample organization, database and bioinformatic recording of sample-associated information, receipt of samples and data from contributing sites, and shipment of requested samples and data to collaborators (Figure III in the online-only Data Supplement).

After contributing sites have evaluated available resources and agreed on sample and data collection and shipment methods with the central site, they can enroll subjects and send samples and data to the biorepository. If a contributing site chooses to send unprocessed whole blood samples for DNA extraction at the central site, the samples should be shipped as soon as possible, ideally on the day they are collected, so that they may be processed quickly. When ready to send whole blood samples, contributing sites may notify the central site, detailing how many samples will be sent and providing the affiliated data. Once this is confirmed and the samples have been properly packed and sent, the contributing site can notify the central site with relevant tracking information, and the central site, will confirm the receipt of the samples, when they arrive, addressing any issues at this time. Sites can also collect and freeze whole blood samples for batch shipment to the central site, although this is not ideal because each freeze-thaw cycle reduces the maximum achievable DNA concentration for each sample.

Contributing sites that choose to send extracted DNA samples are encouraged to establish a timeline for shipment (eg, biannual, quarterly) and desired sample parameters (eg, concentration, volume, tube type, and labeling format) with the central site. When ready to be shipped, the samples may be transferred at the agreed on specifications into the specified container, quantified, and each sample's location in the plate recorded, along with relevant concentration, volume, and phenotypic information. The contributing site may then notify the central site of the shipment, including the completed plate layout for review. Sample labeling is important at this stage to ensure the correct linkage between samples and associated phenotypic information. When the central and contributing sites agree that all necessary samples and information are present, the contributing site will pack the samples according to the International Air Transport Association dangerous goods regulations,¹⁸ using adequate dry ice to ensure that samples do not melt before arrival. For some shipments, specific customs regulations and declarations may apply, along with export or import control laws. Once samples are received by the central site, the samples will be quantified and stored until needed. All relevant data will be kept by the central site in a specifically designed, secure database. After samples are genotyped and their data were analyzed, genetic data may be returned to the contributing site for internal use (Figure). Although these considerations are presented in the context of DNA sample processing and handling, these broad principles and procedures extend to any biological sample type with specific modifications as needed.

Database and Bioinformatics

After sample collection methods are determined, secure storage of both the phenotypic and sample information must be arranged. The US Health Insurance Portability and Accountability Act prohibits all protected health information sharing between the contributing site and the central site and recommends that all samples and data to be deidentified before shipment. Although deidentification specifically requires that data be stripped of common identifiers, a link between the deidentified data set and the fully identified data set may remain at the home institution. Contributing sites are encouraged to

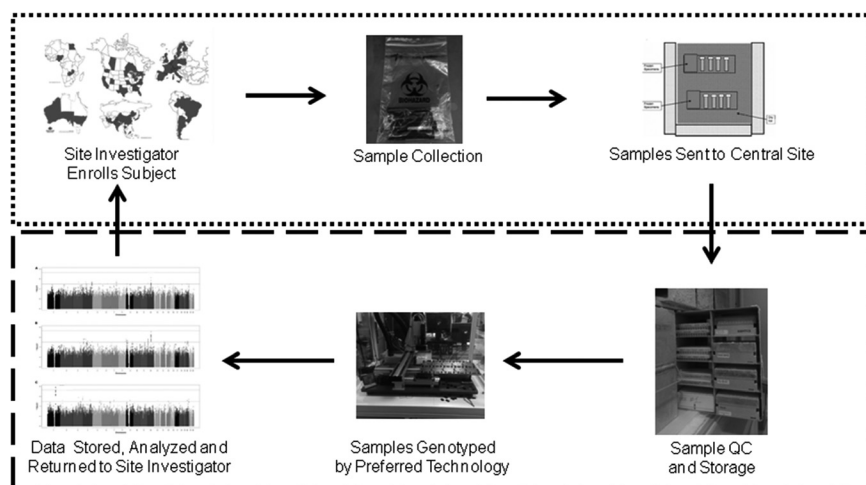


Figure. Biorepository sample collection cycle. Steps in the dotted box are completed at the contributing site, whereas steps in the dashed box are completed centrally. QC indicates quality control.

keep this link at their institution because further phenotypic data may be requested in the future; however, this link should never be stored at the repository. Off-site back-up storage may also be desired as an additional layer of security.

When organizing biological sample data, we have found the following categories useful: collaborating site name, individual ID, alternative site ID, aliquot ID, sample type, concentration (ng/ μ L), volume (μ L), container type, freezer location, sample degradation status, shipment history, and date received. Complications that may arise when storing sample data include linking multiple sample aliquots to 1 individual, recording multiple sample types (DNA, plasma, etc.), ensuring that no aliquot ID is duplicated, and updating of concentrations, volumes, and shipping histories. To address these complications, the central site may use a standard naming convention and storage system.

The last, but perhaps most important, aspect of databases and bioinformatics is sample coding. All individual IDs and sample aliquots should be coded in a uniform manner without any possibility for duplication. The ISGC biorepository has handled this by adding prefixes and suffixes onto sample names, where the first 3 letters of the contributing institution's name is used as a prefix. For example, BOS_0001 denotes an individual from Boston, whereas LUN_0001 denotes an individual from Lund, Sweden. Using this prefix system, multiple institutions can contribute samples with the same ID numbers without causing duplication in the database. However, a single individual ID may have multiple aliquot IDs. To address this, a suffix individualizes these IDs and separates sample types. The suffix system used by the ISGC biorepository comprises the following: a letter is used to distinguish sample types (D=DNA, P=plasma, C=cerebrospinal fluid, S=serum, and R=RNA), and a number is used to identify the sample aliquot. For example, if individual BOS_0001 has 3 DNA sample aliquots, their IDs will be BOS_0001_D1, BOS_0001_D2, and BOS_0001_D3. Although the central site should code each site's samples in a uniform yet unique manner, the contributing site's original deidentified ID should be stored in an alternative ID field to ensure a permanent link between the information about the samples stored at the central site and the sample information back at the contributing site should a need to relink them arise.

Physical Resources

Laboratory resources are essential for the success of any biorepository. Before determining what particular equipment is needed, the central site must determine what services it aims to provide. As a basic example, storing samples requires only a -80°C freezer and a freezer alarm system with emergency back-up power, whereas sample processing and aliquoting require advanced robotics and various laboratory tools. Thus, the central site should address the following questions with its collaborating sites at the outset, before accepting samples.

How many samples will be sent and what are their storage requirements?

- a. What types of samples are being stored? Must they be stored in specific container types? Do they require storage at different temperatures?

Prestorage: will any manipulation be done to the samples?

- a. This may include DNA extraction, sample aliquoting, DNA degradation assessment, or sample dilution.

Poststorage: will the samples be manipulated or altered before they are distributed?

- a. The receiving site may have specific sample requirements, including particular storage containers, plate layouts, and concentration or volume maximum/minimum. However, if the central site is planning to complete projects in-house, it should acquire the necessary equipment independently along with laboratory space to store these tools.

Once these items have been addressed, the central site should acquire the resources needed for their biorepository. The ISGC biorepository based at Massachusetts General Hospital currently has the following tools to support the ISGC samples and ongoing genotyping projects: two -80°C freezers, 2 separate alarm notification systems, departmental back-up freezer support, small and large bench centrifuges, automated 8-armed and multichannel robotic liquid handling systems, DNA extraction kits, multichannel pipettes, single-channel pipettes, degradation gel cassettes/bases/imager and access to a department stock room, which carries a variety of disposable equipment (plates, pipette tips, gloves, etc.).

Of great importance to this equipment's operation is the availability of the central site's staff. Acting as the administrative and laboratory support for a biorepository requires substantial time and effort on behalf of personnel. The central site should assess how much time it will take to run a biorepository successfully and the availability of trained staff to fulfill these responsibilities. For large-scale repositories, robotic automated sample handling may represent an alternative to human sample preparation; despite the initial expense, this may improve efficiency, reduce costs, and eliminate human error in the long term.

The final, perhaps most important, resource in a successful biorepository is a trusting, transparent relationship among collaborators. The whole process of study design, sample collection, linkage to phenotypic data, genetic analysis, and result dissemination cannot be achieved without a willing and able network of coinvestigators who strive toward a common goal. The ISGC as a whole has worked to foster a sense of camaraderie throughout the group, allowing for transparency and trust to form the basis of its operations.

Conclusions

We have detailed the considerations necessary for investigators seeking to participate in a large research biorepository. Current and future ISGC members have the option to retain samples locally or send them to a larger central repository. We encourage all investigators with an interest in enrolling research subjects for stroke genetic studies to follow the procedures we have recommended. We hope the ISGC's experience is useful for enhancing collaborative studies across a range of disease areas.

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SUPPLEMENTAL MATERIAL

Recommendations from the International Stroke Genetics Consortium, Part 2: Biological Sample Collection and Storage

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[Institution Name]
Research Consent Form

Research Tissue Bank

Version Date: [Version Date]

Subject Identification

Protocol Title: [Relevant and Descriptive Name]

Principal Investigator: [Overall Biobank PI Name]

Site Principal Investigator: [Local Institution PI Name]

Description of Subject Population: Individuals seen at [Institution Name]

What is the purpose of this research tissue bank?

We are asking you to participate in a biobank aiming to create a resource for future research.

Researchers at [Institution Name] are studying how genes and other factors affect people's health and contribute to human disease, such as heart and vascular disease, stroke, and other health conditions. To perform this research, we are asking patients to allow us to store their health information and biological samples in the [Biobank Name].

Taking part in this biorepository is up to you. Your decision to participate will not affect your clinical care in any way. Your participation can help us better understand, treat, and even prevent diseases that affect your loved ones, your family's future generations, and the larger community.

Some of the people who are eligible to take part in this study may not be able to give consent to take part because of their medical condition. Instead we will ask the person's authorized representative to give consent. Throughout the consent form, "you" always refers to the person who takes part in the study.

What will I have to do to give samples to the tissue bank?

If you decide to sign this consent form, you are providing your consent to participate in the [Biobank Name]

- You will be asked to donate a blood sample of up to 5 tubes (about 3 tablespoons).
- We may also use blood, urine, cerebrospinal fluid, skin biopsy, or other tissue samples collected as part of your clinical care now or in the future that would otherwise be thrown away.
- We will also look at your medical records now and in the future to update your health information.

[Institution Name]
Research Consent Form

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Subject Identification

- We will store some of your health information in the study database.
- We may ask you questions about your health.
- We may contact you via telephone to get follow-up information about your health status.
- We may also contact you in the future to get additional information and ask if you are interested in joining other research studies.

How are my samples stored?

Staff at the bank will assign a code number to your samples and health information. Your name, medical record number, or other information that easily identifies you will not be stored with your samples or health information. The key that links your identifying information to the code number will be stored securely in a separate file.

Which researchers can use my samples and what information about me can they have?

Your coded samples and health information may be shared with researchers at [Institution Name]. They may also be shared with researchers at other institutions or with for-profit companies that are working with [Institution Name] researchers. Your samples will not be sold for profit. We may use your samples and information to develop a new product or medical test to be sold. The hospital and researchers may benefit if this happens. There are no plans to pay you if your samples and information are used for this purpose.

We will only share information that identifies you with researchers within [Institution Name] who have approval of the [Institution Name] ethics board. We will not share information that identifies you with researchers outside [Institution Name].

In order to allow researchers to share research results, agencies such as the National Institutes of Health (NIH) have developed secure banks that collect and store research samples and/or data from genetic studies. These central banks may store samples and results from research done using [Institution Name] samples and health information. The central banks may share these samples or information with other qualified researchers to do more studies. Results or samples given to the central banks will not contain information that directly identifies you. There are many safeguards in place at these banks to protect your privacy.

For what type of research will my samples be used?

[Institution Name]
Research Consent Form

Research Tissue Bank

Version Date: [Version Date]

Subject Identification

- We plan to do many types of biological and genetic research with your sample. Research using your samples and health information is important for the study of virtually all diseases. Your samples and information may also be used for research on other conditions; for example, as comparisons to other diseases. This could include a wide variety of conditions such as heart disease, stroke, brain injury, diabetes, mental illness, HIV/AIDS, cancer, and others.
- Genetic research may include looking at some or all of your genes and DNA to see if there are links to different types of health conditions. DNA is the material that makes up your genes. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work, and determine physical characteristics such as hair and eye color. Genes are passed from parent to child.
- We may create a “cell line” from your sample that will allow researchers to have an unlimited supply of your cells for future research.
- We may use your cells to create pluripotent stem cells. This type of cell can be used to create different types of tissue, for example, heart, muscle, or lung cells. Your cells might be used in research that alters genes in the cells in order to study different diseases and normal healthy processes. Your cells might be mixed with other human cells, animal cells, or grown in lab animals like mice.
- We may also perform a whole genome analysis on your DNA sample. Usually researchers study just a few areas of your genetic code that are linked to a disease or condition. In whole genome studies, all or most of your genes are analyzed and used by researchers to study links between various factors of health and disease.
- We may share your samples and any cell lines that are created, your DNA sequence information, your health information, and results from research with other central tissue or data banks, such as those sponsored by the National Institutes of Health, so that researchers from around the world can use them to study many conditions. The samples and data will be sent with only your code number attached, not your name.
- It is not possible to list every research project. Also, we cannot predict all of the research questions that will be important over the next years.

[Institution Name]
Research Consent Form

Research Tissue Bank
Version Date: [Version Date]

Subject Identification

How long will my samples and information be kept?

Your samples and health information will be stored in the [Biobank Name] indefinitely.

Can I stop allowing my samples and information to be stored and used for research?

Yes. You have a right to withdraw your permission to participate in the [Biobank Name] at any time. If you do, your samples and your information will be destroyed. However, it will not be possible to destroy samples and information that have already been used or given to researchers. If you decide to withdraw your permission, you should contact the biobank staff in writing:

[Name and Address of Biobank]	Phone: FAX: Email:
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You may also contact the Institute Biorepository to withdraw your permission:

[Investigator Name] [Investigator Address]	Office: Fax:
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Will I get results of research done using my samples?

You may receive a newsletter or other information that will tell you about the research discoveries from the tissue bank. This newsletter will not identify you or describe any of your personal results.

Generally, we will not return individual results from research using your samples and data to you or your doctor. Research using your sample is just a stepping stone in learning about health and disease. Most of the findings that come from studying your sample will not be relevant to your personal health. However, in the future, this may change.

[Institution Name]
Research Consent Form

Research Tissue Bank
Version Date: [Version Date]

Subject Identification

It is important to remember that research results are not always meaningful and are not the same as clinical tests. While you should not expect to receive any results from your participation in this research, if experts from the blood and tissue bank decide that research results from your sample are of high medical importance, we will attempt to contact you. In some situations, follow up testing might be needed in a certified clinical lab. You and your medical insurer may be responsible for the costs of these tests and any follow up care, including deductibles and co-payments. In case we need to contact you about medically important research results from your sample, please also notify the tissue bank staff listed on page 4 if your address changes.

It is possible that you will never be contacted with individual research findings. This does not mean that you don't have or won't develop an important health problem.

In the future, when research results are published, they may show that certain groups (for example, racial, ethnic, or men/women) have genes that are associated with increased risk of a disease. If this happens, you or others may learn that you are at increased risk of developing a disease or condition.

What are the risks to me?

The main risk of allowing us to use your samples and health information for research is a potential loss of privacy. We protect your privacy by coding your samples and health information.

There is a risk that information about taking part in genetic research may be used by insurance companies and/or employers. If you do not share information about taking part in this study, you will reduce this risk.

Research results obtained in this study will not be placed in your medical record unless we contact you with a finding of high medical importance.

We do not think that there will be further risks to your privacy by sharing your samples and whole genome information with other researchers; however we cannot predict how genetic information will be used in the future.

There is a very small risk of bruising or infection from drawing blood similar to what might occur from a routine blood draw that you get for your doctor. Rarely, people feel lightheaded or faint when their blood is drawn.

[Institution Name]
Research Consent Form

Research Tissue Bank
Version Date: [Version Date]

Subject Identification

If I take part in this research tissue bank, how will you protect my privacy?

In general, health information that identifies you is private under federal law. However, you should know that in addition to [Institution Name] researchers the following people or groups may be able to see, use, and share your identifiable health information from the research and why they may need to do so:

- Any sponsor(s) of these biorepositories and the people or groups it hires to help with the biorepositories
- The [Institution Name] ethics board that oversees the project and the [Institution Name] research quality improvement programs
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or organizations that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- While we do not think it likely, under exceptional circumstances, we could be legally compelled to allow law enforcement or national security agencies access to information including genetic data.
- We share your identifiable health information only when we must, and we ask anyone who receives it from us to protect your privacy. However, once your information is shared outside [Institution Name], we cannot promise that it will remain private.

What are the benefits to me?

You will not directly benefit from research conducted on your samples stored in the [Biobank Name]. We hope that research using the samples and information will help us understand, prevent, treat, or cure diseases.

You will not receive payment for your samples.

What are the costs to me to take part in the research tissue bank?

There are no costs to you to participate in the [Biobank Name].

[Institution Name]
Research Consent Form

Research Tissue Bank
Version Date: [Version Date]

Subject Identification

Can I still get medical care within [Institution Name] if I don't take part in this research tissue bank or if I stop taking part?

Yes. Your decision won't change the medical care you get within [Institution Name] now or in the future. There will be no penalty, and you won't lose any benefits you receive now, or have a right to receive.

Taking part in the bank is up to you. You can decide not to allow your samples and information to be placed in the bank. If you decide to take part now, you can change your mind and drop out later.

Whom do I call to answer questions about the research tissue bank?

You may ask more questions about these tissue banks at any time. The [Biobank Name] staff members are available to answer your questions or concerns.

The person in charge of the [Biobank Name] is [Investigator Name]. He can be reached from Monday - Friday 9a – 5p at [Investigator Phone Number].

Whom do I call if I have concerns about my rights as a research subject?

If you want to speak with someone **not** directly involved in the tissue bank project, please contact the ethics board office. You can call them at [Phone Number].

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research tissue bank
- A complaint about the research

Also, if you feel pressured to take part in the research tissue bank, or to continue with it, they want to know and can help.

[Institution Name]
Research Consent Form

Research Tissue Bank
Version Date: [Version Date]

Subject Identification

Informed Consent and Authorization for Collection of Samples and Health Information for Research

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent

Date/Time

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject

Date/Time

[Institution Name]
Research Consent Form

Subject Identification

Research Tissue Bank
Version Date: [Version Date]

Signature of Guardian or Authorized Representative for Adult:

I give my consent for the person I am authorized to represent to take part in this research study and agree to allow his/her health information to be used and shared as described above.

Print Name (check applicable box below)

- ☐ Court-appointed Guardian
☐ Health Care Proxy
☐ Durable Power of Attorney
☐ Family Member/Next-of-Kin

Signature

Date/Time

Relationship to Subject: _____

[Institution Name]
Research Consent Form

Research Tissue Bank
Version Date: [Version Date]

Subject Identification

Consent of Non-English Speaking Subjects Using the “Short Form” in the Subject’s Spoken Language

Statement of Hospital Medical Interpreter

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Hospital Medical Interpreter

Date/Time

OR

Statement of Other Individual (Non-Interpreter)

As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject’s own language, and that the subject was given the opportunity to ask questions.

Name

Date/Time

Consent Form Version:

Figure I: Template informed consent form for participation in a research biorepository.

TISSUE REPOSITORY PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the relevant information. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

[Investigator Name]

PROTOCOL TITLE

[Relevant, descriptive title]

FUNDING

[Funding Agency]

VERSION DATE

[Date of Submission]

SPECIFIC AIMS

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

A. Collection and Storage

1. To collect and store biological samples [such as DNA, plasma, blood cells, and cerebrospinal fluid (CSF)], along with relevant medical information, from adult inpatients and outpatients seen by physicians in the [Clinical Unit Name] (including those patients with brain injury of any mechanism, including vascular, inflammatory, traumatic and neurodegenerative).

B. Future Research

2. To make quality, characterized samples and related data available for future studies, including Genome Wide Association Studies (GWAS), genomics, and biomarker research.

3. To use these samples and related medical information to answer research questions aimed at understanding the genetics and underlying biology of acquired disease and injury to the brain, heart and blood vessels with the express purpose of advancing the search for effective modalities for prevention, treatment, and recovery.

4. To develop additional operational infrastructure to support this project across the [Clinical Unit Name] and divisions, including (1) tracking of patient consent, (2) management of collection and sample processing processes, (3) sample inventory and QC/QA processes, and (4) release of materials to investigators for further research.

BACKGROUND

Justify why collection of these tissues is warranted scientifically. Summarize briefly the knowledge to date about the disorder, or condition under study. Describe the general directions for the research. If samples are stored for as yet undefined or general uses, please describe the *types* of research expected, providing examples.

The demands for highly characterized human samples have grown by orders of magnitude in recent years, given the adoption of high-throughput techniques in genotyping and analysis of protein and other markers in fluid samples and tissues.

The cost of obtaining consented samples thus frequently represents the most expensive aspect of performing biomedical research. In many cases, individual investigators or groups create one-off processes that are inefficient and lack economies of scale to be able to approach the consent of patients and collection of materials for research.

The construction of this biorepository aims to address these needs across the [Institutional Department Name] research enterprise by utilizing existing and, when necessary, developing new operational and IT infrastructure to support the consent of patients and the collection of dedicated samples for a biorepository available to our [Institutional Department Name] investigators.

TYPES OF TISSUES TO BE BANKED

Explicitly list what types of tissues will be collected, listing all, for example: (a) excess material from clinical operative procedures (e.g., tumor after pathologist's sampling completed); (b) prospectively collected human material/tissue, either normal or pathological, taken at the time of a clinically planned procedure (e.g., cardiac biopsy at catheterization or open heart surgery, extra biopsies at endoscopy, additional intestine at gastric bypass, or normal fat or skeletal muscle at surgery, extra CSF at LP, extra blood at phlebotomy); and/or (c) prospectively collected human material/tissue obtained during a procedures performed solely for research, e.g., blood, urine, saliva, breast milk, skin, muscle, semen samples, or cells from cheek swabs. Explicitly state whether immortalized lymphoblastoid cell lines, fibroblast cell lines or tumor cell lines are planned. Inexhaustible cell lines are considered of greater risk to confidentiality than finite samples like excess tumor that will be eventually consumed entirely by research.

Blood:

Blood will either be collected prospectively at the time of a clinically planned procedure or prospectively during a procedure performed solely for research. After informed consent is obtained, the patient will be asked to donate a one time blood sample of up to 5 tubes (about 50 ccs or 3 tablespoons). A portion of each blood sample will be used to generate a DNA sample, and the remainder will be used to separate out plasma, peripheral blood cells, and/or serum for future research studies, including but not limited to metabolomics, proteomics, biomarker measurements, and bioenergetic assays.

Cerebrospinal fluid:

Cerebrospinal fluid may be collected prospectively from the subset of patients who have an external ventricular drain (EVD) placed as part of their clinical care. The standard clinical protocol for EVD includes the drainage of CSF externally into a collection bag. Once the volume of CSF drainage is recorded, the CSF is typically discarded. The collection of CSF will be coordinated with the subject's primary treatment team. At this time, CSF banking will not occur in subjects who do not have CSF collection planned as part of their clinical care. CSF samples will be obtained by a neurosurgeon, neurointensivist, or trained nurse practitioner.

Excess/Discarded Tissue:

This repository will also aim to collect and store excess/discarded tissue from clinically indicated procedures such as blood draws and skin biopsies. The tissue collected will include skin, muscle, and other tissue as available. From time to time, clinically indicated procedures such as skin biopsies could be performed, which would allow for the collection of additional tissue types. The only tissue collected will be what is in excess of clinical need and will be cultured and/or frozen for future use.

Use of other research samples:

Samples that have previously been collected as part of another research protocol may also be included in this repository as is consistent with subjects' original consent or separate IRB approval. Before including these samples in the repository, consent forms from the protocol under which the samples were collected will be submitted to the [Institution Name] IRB for approval. In the case of samples collected under protocols approved by non-[Institution Name] IRBs, the local IRB may instead submit an assurance letter attesting that inclusion of these samples in the biorepository is consistent with the original consent form signed by subjects at the time of sample collection.

Tissue collection for the repository will potentially include immortalized lymphoblastoid cell lines, fibroblast cell lines, or tumor cell lines.

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects who provide tissue samples at [Institution Name] performance sites. Specify how potential subjects will *initially* learn about the possibility that they could provide samples to this tissue repository. Specify how, when, where, and by whom, subjects will be approached about providing samples to this tissue repository.

Inclusion Criteria:

- Adult ≥ 18 years of age
- Subject or surrogate signs the written informed consent form.

- Subject is willing to have blood drawn for storage of samples in a research bank
and/or willing to have their discarded samples collected for inclusion in a research bank.

Exclusion Criteria:

-None

Recruitment Procedures

Subjects will be recruited within the variety of inpatient and outpatient settings of the [Institutional Department Name]. Residents, fellows, attending physicians, health care providers, and/or non-clinical study staff will evaluate the eligibility of each patient, based on the inclusion/exclusion criteria. Treating clinicians will be consulted before eligible patients or their surrogates are approached by repository study staff to discuss the repository. Please note that determining capacity for a subject to provide consent will be consistent with their clinical ability to make medical decisions. When in doubt, the clinical team will be consulted. Research coordinators will not be making this decision alone. Informed consent is obtained in standard fashion and a copy of the signed consent will be offered. As part of the consent process, consultation with a physician investigator will be proactively offered.

Please note that there will not be regular recruitment of patients in the ER or ICUs. Rather recruitment will only be undertaken should a special case of interest present, (e.g. unique brain injury) where the treating physician for that patient is within the [Institutional Department Name] and believes that a sample contributed to the biorepository will be of particular scientific merit.

Expired patients

If a potential subject expires before consent is possible, we will attempt to obtain blood sample(s) for analysis. These samples are routinely drawn for clinical purposes and lose all clinical utility after a patient's death.

Samples from other research studies and outside institutions

The [Institutional Department Name] participates in the International Stroke Genetics Consortium (ISGC), a collaborative network of approximately 50 centers from around the world. A substantial proportion of these centers recruit patients with cerebrovascular disease for collaborative genetic studies. Under this protocol [Central Biobank Institution Name] will receive these biospecimens and retain them within the biorepository. All subjects will provide informed consent using human studies protocols approved by the local institution. [Central Biobank Institution Name] investigators will require outside institutions to provide either translated consent form(s) that will be reviewed by the [Central Biobank Institution Name] IRB or completed IRB verification letter before accepting any samples from outside institutions.

Phenotypic data to be included:

In addition to the aforementioned samples, related phenotypic data will also be included, thereby increasing the value of our biorepository (e.g. age, gender, ethnic background,

diagnosis, clinical features, presence of any co-existing conditions, pathology, imaging, and other test results, surgery reports, and family history).

Clarify whether there are existing collections or samples that will be “grandfathered” into this bank. Describe the “consent status” of those samples, i.e., what kind of consent was provided by those from whom such older stored samples were collected. Include a copy of the consent form, when applicable.

No previously collected samples will be “grandfathered” into this repository at this time.

Provide details of remuneration of research subjects, when applicable.

No remuneration is anticipated for participation in this repository.

CONSENT PROCEDURES

Explain in detail how, where, and by whom informed consent is obtained from the subject providing samples. Describe timing of consent, i.e., 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 or a physician investigator will be available for consultation or questions, when informed consent is obtained by someone other than the principal investigator or physician investigator.

[Institution Name] patients

All members of the study staff will share in the responsibility of obtaining informed consent. Consent will be sought once the patient is deemed eligible to participate in the study. Physician investigators will decide whether a subject is capable of providing informed consent. If there is any doubt, a member of the subject's clinical care team will be consulted. Please note that determining capacity for a subject to provide consent will be consistent with their clinical ability to make medical decisions. As previously stated, when in doubt, the clinical team will be consulted. Research coordinators will not be making this decision. If the patient/surrogate is interested in learning more about the study, a repository staff member will present the details of the repository study. Investigators and/or study staff will answer any questions and address any concerns raised by potential subjects and/or their family members. Subjects and their families will then be given as much time as needed to consider participation. A physician investigator will be available by page during the consent process and consultation with a physician investigator will be offered. In the case of surrogate consent, if the patient is conscious, verbal assent will be obtained and noted in the repository records. If the patient expresses dissent, the repository staff will respect the patient's wishes and cease recruitment.

Samples from other research studies and outside institutions

In the event that samples will be obtained from other research studies or outside institutions, consent forms from the protocol under which the samples were collected

will be submitted to the [Institution Name] IRB for approval. In the case of samples collected under protocols approved by non-[Institution Name] IRBs, the local IRB may instead submit an assurance letter attesting that inclusion of these samples in the biorepository is consistent with the original consent form signed by subjects at the time of sample collection.

Repository staff consent training

Staff obtaining informed consent will observe the consent process several times with an experienced research coordinator, as well as with a physician. After observing the process, the research coordinator will next lead the informed consent process under the supervision of the trainer(s). This training will be completed before the research coordinator begins recruiting subjects for the repository on his/her own, and will ensure that the research coordinator is adept at obtaining informed consent from potential subjects or their surrogates.

As part of their continuing education, [Institution Name] study staff members who do not have formal medical training (such as study coordinators), will have the opportunity to complete genetics education, as well as human subjects research trainings, offered by the [Institution Name] and others. These classes specifically address some of the regulatory and ethical challenges in clinical research, including consenting for genetic research studies.

When applicable, explain how provision of samples to more than one repository is discussed with subjects. Typically each repository has a specific consent form.

All samples will be stored in [Institution Name]-based freezers. As stated in the consent form, a portion of the blood samples collected as part of the biorepository of the [Institutional Department Name] will be given to the [Central Biobank Name]. These samples will also be stored in freezers at [Institution Name] and will be subject to the same privacy and security measures.

In general, the human research council requires researchers to obtain the informed consent of the individual from whom the human material/tissue was obtained. Surrogate consent is usually not appropriate since there are no direct benefits to the individual. If you propose to include subjects who are unable to give consent due to age (minors) or current physical/mental condition, discuss this issue in detail. Indicate from whom consent will be obtained, for example, from parents/guardians, legally authorized representative, next-of-kin, etc. If you choose to include such subjects, explicitly rationalize the inclusion of subjects unable to consent on their own behalf, based upon risk/benefit considerations.

It is anticipated that a significant proportion of potential subjects will be able to provide informed consent for themselves. However, since the aim of the biorepository is to promote research of the genetic and molecular mechanisms of disease *and* injury, we are looking to provide a tissue and phenotypic resource that represents the full spectrum of the population for whom we care. In some cases this may include cognitively impaired patients, such as those with severe brain injury. As a result, we must also seek to enroll adults with impaired decision-making capacity. Failure to

include this population would result in a true representation of persons with these conditions being unavailable for research, biasing any knowledge gained from the repository against the patients who have suffered the most severe forms of brain injury, thereby limiting the generalizability of research findings.

If a subject is making his or her own medical decisions, this is typically taken as evidence that (s)he is able to consent to this study. If there is any doubt, a member of the subject's clinical care team will be consulted. When a subject is incapable of providing consent, we will approach the subject's surrogate for consent. A surrogate can be a court-appointed guardian with authority to make health care decisions, a healthcare proxy, or person with the power of attorney, a spouse, adult child, or another family member. If surrogate consent has been obtained but the subject dissents, we will honor the subject's request and withdraw the individual from the study.

Subjects may be contacted for additional follow-up phone calls. Because we anticipate that a portion of subjects will be enrolled through surrogate consent, we will utilize the follow-up phone calls as an opportunity to confirm subjects' willingness to continue participation. Subjects who were consented through surrogate consent will have the opportunity to either continue participation or to withdraw from the study.

As with all potential subjects, we will explicitly delineate to the subject's family/surrogate the difference between research and treatment, and distinguish the study staff from the clinical treating team throughout the consent process. We will explain that any tissue received from the subject will be stored in a repository, to be used in future research, and will not be used to aid in the subject's clinical treatment except in the unusual circumstance that we uncover a finding of high medical importance. In such an instance, the IRB will be contacted to review the situation before proceeding.

If [Institution Name] investigators will not be obtaining informed consent from all subjects, clarify how investigators who are obtaining consent will provide you with documentation of consent and IRB approval of the relevant protocol and consent forms. Provide a copy of the IRB approved-consent form(s), when applicable.

When samples will be obtained from other research studies or outside institutions, consent forms from the protocol under which the samples were collected will be submitted to the [Institution Name] IRB for approval. In the case of samples collected under protocols approved by non-[Institution Name] IRBs, the local IRB may instead submit an assurance letter attesting that inclusion of these samples in the biorepository is consistent with the original consent form signed by subjects at the time of sample collection.

WAIVER OF INFORMED CONSENT/AUTHORIZATION

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

We will obtain informed consent from each human subject or surrogate when necessary. The only exceptions pertain to situations in which eligible acutely ill patients die before they can be enrolled (not human subjects) or excess samples from other approved research studies are obtained.

Death

Due to the nature of the population being recruited, potential subjects may die acutely after they are admitted to the inpatient service, but before they are able to provide consent. Failure to include expired subjects in the repository would serve to create an inaccurate representation of the patient population and would bias any knowledge gained from the repository against the patients who have suffered the most severe forms of brain or cardiovascular injury.

Although deceased individuals do not meet the definition of human subjects and thus the consent regulations do not apply, we are requesting a waiver of the HIPAA Authorization to obtain a blood sample, if available, and to access protected health information solely for research purposes. These samples are routinely collected for clinical purposes on admission and lose all clinical utility once a patient has expired. We are requesting a waiver of the HIPAA Authorization for these subjects to maintain identifiers for decedents for the purpose of correlating future findings with phenotypic information that may exist in medical records.

Excess samples from within [Institution Name]

Some of the excess samples that we may wish to include in the repository may have previously been collected for research as part of another approved protocol, and the subject may have been lost to follow up. Therefore, it would not be possible to contact the subject to obtain consent for this repository. Since their samples and related medical data will continue to have great utility, we would like to include them in our biorepository. As the risk to the subject's privacy will be no more than minimal (only data that is already in the subject's medical record), the waiver of consent will not adversely affect the rights and welfare of the subjects.

In the case that consent for future use was not expressly obtained in the initial consent form or the consent form is inadequate the samples will be included with minimal clinical data, such as gender, age, diagnosis, etc. We will utilize a 30 day escrow period to obtain the necessary additional information, after which the data and samples must be stripped of all identifiers and/or key to the codes linking to identifiers. For any [Institution Name] feeder studies, the consent forms will be submitted to the IRB for review to ensure the consent form adequately covers the repository uses.

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

The repository would be of limited utility if we were not able to include expired subjects and excess samples from other studies. Research findings could not be generalizable if

we were not able to conduct research on those samples with some health information which indicates their condition at the time of the collection so that we may further medical knowledge about that patient-specific case/condition.

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

This tissue storage presents no more than minimal risk of harm to the aforementioned groups of subjects because the storage of samples from expired subjects and other studies, will contain only limited PHI or information that is already part of the subject's medical record, and will be protected under strict policies and procedures preventing the release of any identifiable subject data.

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

Obtaining samples and data from an expired patient or other studies will not adversely affect the patient's rights. Samples and information obtained from the patient will be protected, and identifying information will not be shared with any unauthorized persons.

4. Explain how the identifiable health information that has been collected and stored will be protected.

Samples and information obtained about the aforementioned subject groups will be stored and protected according to the same strict policy that applies to all of the subjects enrolled in the study. All identifying information recorded on paper will be stored in a secure office that is only accessible to study staff. Biospecimens (including plasma, serum, peripheral blood cells, DNA and/or CSF) will be stored for future use in separate tubes, which will be stripped of all identifying information and replaced with Study IDs. The key linking this code with the identity of each subject is electronically maintained in a password-protected database stored on a password protected network drive, accessible only to study staff.

5. Explain when the identifiers (such as the HIPAA identifiers listed above or the code linking the tissue to identifiable health information) will be destroyed at the earliest opportunity, for example, when the human material/tissue is used up.

Data and biospecimens will be stored for as long as the tissue repository exists.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. List inclusion and exclusion criteria for subjects (bulleted lists are

preferred). Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

No one group will bear an unreasonable share of the burden of the research. This repository aims to recruit any adult within the [Institution Name] seen by physicians within the [Institutional Department Name] All patients who meet the inclusion/exclusion criteria for the repository may be asked to consider participation.

When enrollment is limited to specific groups (e.g., study of sickle cell anemia will not enroll Caucasian subjects), provide the scientific basis for the study population. When the medical condition under study exclusively or disproportionately affects one group of individuals, please describe this propensity. Describe how this will affect your enrollment of subjects across the diverse spectrum of patients cared for by our institutions. Address whether any one group will bear a disproportionate share of the burdens of research or, whether the benefits, to the extent anticipated, will be distributed fairly. Comment on efforts to enhance the enrollment of women and minorities, including subjects who do not understand English.

Since patients seen and treated within the [Institutional Department Name] include male and female adults of all ethnicities, all patients fulfilling the inclusion criteria and receiving treatment within [Institution Name] may be enrolled. We will not discriminate based on gender, race, or ethnicity.

For non-English speaking patients, the study investigators will provide a written consent document in a language understandable to them and an interpreter fluent in both English and the subject's spoken language will be provided. We confirm that we will use the short form consent form for non-English speaking patients

OPERATING POLICIES AND PROCEDURES OF THE REPOSITORY

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

Collection, processing, and storage of samples

Following the signing of the informed consent form, the subject will be assigned a study code number for use in linking specimens and corresponding medical information. The samples will be assigned a barcode for tracking and the code linking the identity will be electronically maintained in a password-protected database stored on a password protected network drive that is only accessible to repository staff.

After a subject has enrolled, blood collection will be performed. Discarded tissue from clinically indicated medical procedures or surgeries will be collected from any subject as

available and will not in any way alter clinical care.

Samples may be used for the creation of iPS cell lines.

All biospecimens will be processed by staff within laboratories at [Institution Name].

The samples will be stored in freezers located in [Central Biobank Name] laboratories for an indefinite period of time. Genetic and plasma material stored for future use is kept in separate tubes, which have been stripped of all identifying information and replaced with a randomly assigned code. The key linking this code with the identity of each subject is electronically maintained on a password-protected database stored on a password-protected network drive, and is accessible only to repository staff. Some tissues collected will be used up through the course of study whereas others (i.e. cell lines) will provide a theoretically inexhaustible source of tissue for future study. Samples will be stored until the repository is no longer in use, at which time any remaining samples will be destroyed.

Collection and storage of relevant phenotypic information

Corresponding clinical data will be obtained through discussion with the subject or surrogate and review of the subject's electronic medical record or hospital medical record. The signing of the consent form document will serve as consent to review records within [Institution Name]. For individuals receiving their care outside the [Institution Name] system, subjects may be asked to sign a medical record release form to obtain records from local providers and hospitals.

Any identifying information recorded on paper will be stored in a secure office that is only accessible to study staff. No indication of participation will be placed in a subject's medical record.

Data to be recorded include age, gender, ethnic background, diagnosis, clinical features, presence of any co-existing conditions, pathology, imaging, and other test results, surgery reports, and family history.

The repository team will include a data manager who will manage the database that links the subject with their random study code number, blood and tissue sample numbers, sample storage location, and corresponding clinical information. This database will be maintained on a department IT-supported password-protected computer. The PI, the study coordinator, and those who are in charge of assigning study-related codes will be the only individuals with the password to this database.

Processes for distribution of tissues: Clarify the process by which other investigators may request tissue from the repository, if proposed. Describe who oversees tissue 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 tissue. Describe what materials are provided to requesting researchers, and what health/medical information accompanies tissue or

samples distributed by the repository. If tissue/samples will not be provided to other investigators, but will be limited to one research group or laboratory, so state. Note that any release of *directly identifiable tissue or directly identifiable health information, or a key to the code linking the tissue directly to an individual* requires a separate, IRB-approved protocol. Clarify who at the repository will assess tissue requests and ensure that, where necessary, there is a current IRB-approved protocol covering the proposed research. Distribution of tissue that is coded, but not directly identifiable, when the recipient researcher will not seek to identify the individual from whom the tissue was 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 sample(s). Such coded human material/tissue 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 samples were derived. Provide a copy of a formal letter or form that recipient investigators will be asked to sign for such tissue distributions.

The second and third aims of this repository seek to use these samples and related medical information to answer research questions aimed at understanding the genetics and underlying biology of disease and injury affecting those patients seen and treated within the [Institutional Department Name]. As a result, there will be several mechanisms for accessing the samples and data for research. Please note, where personal identifiers are linked to the samples/data, they will always be secured by the repository data manager. Unless separate IRB approval is obtained, under no circumstances will the subject's personal identifiers be provided to non-repository co-investigators thereby maintaining the subject's privacy and confidentiality. The repository will distribute coded data/samples for purposes that are consistent with the repository aims or consent form used to obtain the samples, such that IRB approval is not necessary. In this case, the requesting investigator will sign an agreement stating that he/she will never attempt to identify subjects.

1) Repository co-investigators

- Request submitted to repository PI and repository governing body
- Once approved, if not already on protocol, added via amendment
- Co-investigator granted access to coded samples and data for their research purposes

2) Other [Institution Name] Researchers

- Request submitted to repository PI and repository governing body

Once approved by the PI, but before the release of the coded/non-identifiable samples, all necessary IRB approvals will be confirmed. If the secondary user does not require identifiable information, and has no IRB approval to obtain such information, the requesting investigator will sign an agreement stating that he/she will never attempt to identify subjects.

3) Academic Collaborators outside of [Institution Name] (e.g. ISGC)

- Request submitted to repository PI and repository governing body.
- As part of the approval process, the repository PI will confirm that there is a current IRB-approved protocol in place for any groups requesting access to the samples. Before release of the coded samples, consent forms will be reviewed and all necessary IRB approvals will be confirmed.
- No directly identifiable tissue or directly identifiable health information will be shared with requesting investigators outside of the study staff, unless approved by IRB review. Once a request has been assessed for all of the above components, the requesting PI will be required to sign the IRB recommended Letter of Agreement for transfer of coded samples which will be kept on file.

If future proposed research is inconsistent with the extent of research originally described in the consent form, we will seek separate IRB review.

Re-contact of subjects providing biological samples to a repository: In general, investigators are advised to plan ahead carefully and describe potential uses and sharing of repository 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 is not prohibited, but it may be time consuming, and may or may not be practical, welcomed by, or useful to, subjects. Research results may not be clinically useful or validated, and may not be ready for return to patients or physicians. It is often most acceptable to describe the types of research that will be performed and indicate that research results will not be returned to subjects or physicians. If it is anticipated that subjects will be re-contacted by representatives of the tissue repository, 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 an option for “no re-contact” 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.

In addition to the samples and information that subjects provide us with at the time of consent, we also plan to gather outcome data from subjects. This follow-up information has the potential to be of great scientific utility for researchers who will perform analyses on the repository. This outcomes portion of the study consists of contacting subjects by telephone at certain intervals after their inclusion in the repository. At every follow-up call, we will confirm the subject’s willingness to continue their participation for as long as they are willing and/or able. Obtaining follow-up outcome data is critical for assessing longer term health, functionality, and recovery, particularly in subjects who have experienced severe injury or illness.

Subjects who are originally consented through surrogate consent, and are re-contacted for follow-up, will be asked to confirm their willingness to continue their participation if they are cognitively able. Subjects may also refuse the follow-up interviews at this time.

The verbal confirmation of continued participation or refusal of follow-up will be noted in the subject's file.

The subject or surrogate will be asked standard follow-up information regarding the subject's physical and psychological condition, their level of functional independence, and any new information pertaining to the subject's condition. If the subject is unable to participate in the phone interview because of cognitive status, the patient's surrogate or family member will be asked to provide follow-up information on behalf of the subject.

Because this is a tissue repository and not a study that will immediately produce clinically relevant data, subjects will not be provided with any research information or results upon re-contact. Similarly, we do not anticipate any need for counseling or notification of any third parties regarding the subject's participation in the repository.

Clarify with whom tissues samples will be shared. Possible options include: (a) only within [Institution Name]; (b) only with academic collaborators; (c) with academic and commercial (for-profit) collaborators. If samples will be shared with collaborators at for-profit companies, please state this explicitly. Investigators are reminded that provision of samples to for-profit collaborators requires the existence of a bona fide intellectual collaboration between the [Institution Name] investigator and an individual or group at the for-profit site, and a Materials Transfer Agreement. Comment upon fees assessed for shipping or preparing samples, and justify these charges.

The tissue samples will be maintained within [Institution Name].

Tissues and data from the repository will only be shared with other academic, non-profit institutions. No collaboration with for-profit companies is anticipated. All investigators seeking to gain access to the repository must first demonstrate that their research interests are relevant to the central theme of the repository. Investigators must also complete all required IRB documentation before samples and information will be released.

In the event that a commercial, for-profit, collaboration is sought, a bona fide intellectual collaboration between the PI and an individual or group at the for-profit site and a Materials Transfer Agreement will be required. For all researchers requesting samples, the IRB recommended Letter of Agreement must be signed prior to our releasing tissues and information.

The fees for the processing and storage of samples will be paid by the study. Investigators requesting a sample will only be assessed a fee for shipping, which is reasonable as the bank will absorb all other costs for creating and maintaining the bank.

Data may be shared with a central repository in the future (e.g. NIH dbGaP) and separate IRB approval will be sought at that time.

PRIVACY AND CONFIDENTIALITY

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.

All subjects will be assigned a study code number upon enrollment to be used in linking specimens and corresponding clinical information. The key to this code will only be available to the principal investigator, the study coordinator, and the staff members who assign study codes and will be kept in a department IT-supported, password-protected computer file. Subject files containing all paper documents with identifying information will be kept in a secure office. All study staff have completed the required human subjects training and have experience in human subjects research.

Phenotypic and clinical information will be entered into a password-protected database. Only the principal investigator, study coordinator, and staff who assign code numbers will have the password to this database. Any discarded papers or computer printouts related to the repository will be shredded. Information about participation or results of any studies will not be disclosed to subjects or be filed in medical charts. Further, any research results generated will not be disclosed to referring physicians, family members, employers, or other third parties in order to minimize risks to a subject's privacy, employment, and insurability.

No non-clinical charges will be billed to insurance companies or to subjects for this study.

When distributed to researchers, samples will either be coded or anonymized by the study staff. Samples will never be shared with any personal identifiers and will be labeled by code number only (unless they are sent anonymized). The data manager will not provide the key to the code to any other researchers without a separate IRB approved secondary use protocol.

As information from any future research will be returned to the subject or a family member only in the rare case of a finding of high medical importance, there is no foreseeable increased potential for psychosocial risks.

Because this study will store PHI on consented subjects, there exists a small risk of loss of confidentiality and privacy. Confidential medical information could be disclosed or discovered by mistake (due to human error) and could influence insurance companies or employers. Safeguards are in place to minimize these risks to the extent possible including the coding of all samples upon receipt, keeping the key to the code in a password-protected computer file with limited staff having access to the key, not including any study documents or results in a subject's medical record, and storing

samples and health information in a secure fashion.

EXPECTED BENEFITS

It is not expected that subjects providing tissue for repositories will derive personal health benefits as a result of their contributions to tissue 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 tissues in this repository.

Study participants will not experience any direct individual benefit. However, it is hoped that (1) a better understanding of the possible clinical, circulating, and genetic risk factors identified as a result of analyses of data and tissue collected for this repository will eventually lead to improved understanding of disease and injury and (2) the advance of the ability for investigators to more efficiently locate samples of interest from a diverse repository will be achieved.

FORESEEABLE RISKS AND DISCOMFORTS

Risks to privacy and confidentiality should be discussed above. 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.

Risks of blood draw include soreness, bruising, dizziness, or rarely infection or fainting.

Tissues (skin, muscle, bone, CSF etc) obtained prospectively from clinically-indicated surgeries after necessary material has been retained for diagnostic purposes will not incur additional risk to subjects.

Breach of confidentiality is the greatest risk associated with this banking project. Confidential medical information could be disclosed or discovered by mistake (due to human error). This information could influence insurance companies or employers. To help prevent disclosure, information about subject participation and the results of any future research will not be placed in the subject's medical records. Samples and data will be coded and the key will be kept in a separate locked file and/or double password protected computer. No information will be released or published in a way that would indicate individual participation in the banking project.

Information about participation in a genetic study may influence insurance and/or employers regarding a subject's health status. It will be discussed with subjects that refraining from discussing information about participation in a study with others will help to minimize these risks. Although every effort will be made to keep a subject's participation confidential, the investigators cannot guarantee absolute confidentiality.

These potential risks are clearly explained to the subject at the time of consent, and subjects are advised that they are free to withdraw from the study at any time. No information generated as a part of this study will be returned to subjects or become a

part of the subjects' medical records except in the unusual circumstance that we uncover a finding of high medical importance. In such an instance, the IRB will be contacted to review the situation before proceeding.

MINIMIZATION OF RISKS

Minimization of risks to privacy and confidentiality should be discussed above. Describe here how any additional risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Venipuncture will be combined with clinically indicated procedures whenever possible so that there is no added risk for individuals who choose to participate in this research. All data recorded on paper will be kept in a separate research file for each subject and will be stored in a locked file cabinet in a locked office. All electronic data will be stored on password-protected workstations. Samples will be stripped of identifiers and assigned a unique identification number. The key linking this identification number with the identity of individuals will be secured in a database stored on a password-protected workstation. All identifiable data will only be accessible to study investigators and staff. Finally, no record of participation in this study will be placed in an individual's permanent medical record.

DATA AND SAFETY MONITORING

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.

The investigator and study staff themselves will perform safety monitoring. All adverse events will be reported according to human research committee policy. The principal investigator and study staff are responsible for monitoring study documentation and assuring that all study procedures are done in accordance with the protocol. All patients admitted to [Institution Name] will be treated according to the standard of care at our institution, regardless of their decision to participate in this repository.

Figure II: Template protocol summary for a research biorepository.

SOP: Shipping Samples to the Central Site

Purpose: To provide instructions on shipping DNA or Frozen Blood samples to a central biobank site

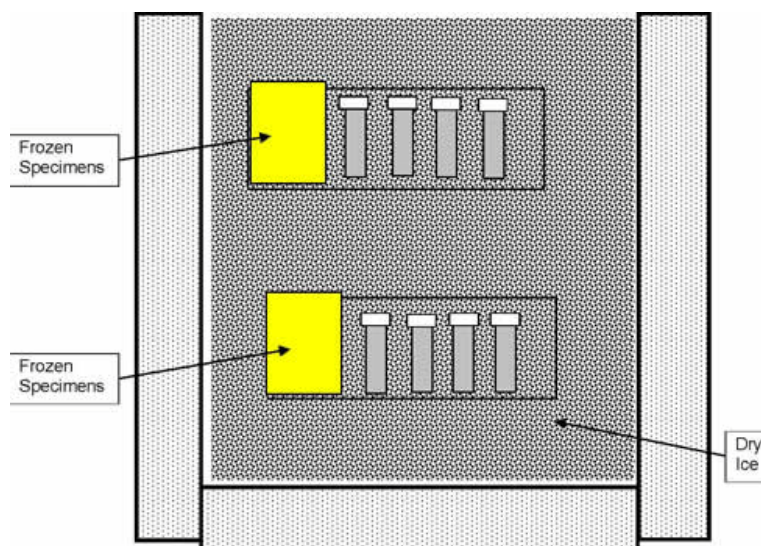
Step 1: Contact Lab to notify them of Shipment

1. E-mail the Lab's technician (Name, email@email.edu) to notify them of your sample parameters:
 - a. Sample Type (DNA or Frozen blood)
 - b. Number of samples
 - c. Estimated shipping date
2. If not already provided, please request the data points needed for phenotype files. The lab tech will e-mail you both an excel sheet of desired data-points and a word document to explain the coding. Please e-mail the completed phenotype file to the lab tech on the day of shipment.
3. Please ship samples only on a Monday or Tuesday, **do not send shipments on Thursday or Friday** (we cannot accept packages on weekends and the samples could be unusable by Monday).

Step 2: Shipping Samples

1. *Before you begin, please refer to UN 3733 regulations and IATA packaging Instruction 650 regarding the shipment of dry ice and other biological substances (such as DNA and blood).*
 - a. Summary of regulations: http://www.ncsu.edu/ehs/dot/Bio_shipping.pdf
2. Based upon the shipping parameters, gather the supplies needed for shipment, and pack the box according to **Figure 1**. Please note that it is highly preferred that samples be shipped in a freezer-box. Please wrap a rubber band around the box to prevent the lid from falling off.
 - a. Shipping Supplies: Cardboard shipping box, Styrofoam box (if using Dry Ice), appropriate FedEx form (Domestic or International Air Waybill), Plastic FedEx Form holder, 2 Dry Ice stickers (for biological samples), UN 3733 sticker

Figure 1: Frozen Shipping Container



3. When packing the Styrofoam box:
 - a. Please use a 1:3 ratio of samples to Dry Ice. Please make sure to place a 2-inch layer of dry ice in the bottom of the Styrofoam box before placing the samples inside. It is very important that the dry-ice does not evaporate before the samples reach their destination – the more dry ice, the better.
 - i. Note: Pellet dry ice is preferred. Block dry ice must be reduced to small pieces (1"-2") to minimize the chance of damage to samples.
 - b. Make sure to enclose the freezer box containing the samples in a larger plastic bag and tape the Styrofoam box shut once filled with dry ice. These packaging regulations are set-up by the United Nations and International Air Transport Association.
4. Create a unique spreadsheet for each Sample Box that describes the contents. Please make sure the spreadsheet includes the points below and email to lab tech on day of shipment.
 - a. Box Name (As it appears on physical box)
 - b. Box Position
 - c. Sample ID (As it appears on physical sample, if labeled)
 - d. Plated Concentration
 - e. Plated Volume
 - f. Gender
 - g. Status (case/control)
5. Ship OVERNIGHT EXPRESS and send to the address below
 - a. Lab Technician Name
Institution Name
Street Address
City, State, Country, Postal Code

Step 3: Document Shipment and Contact Collaborators

1. On the day of shipment, e-mail the Lab tech with the information listed below. They will e-mail you confirmation when they receive the samples at their destination.
 - a. FedEx tracking number
 - b. Phenotype file
 - c. Sample Identification spreadsheet (Steps 2-5).

Figure III: Standard operating protocol for sample shipment to a biorepository.

Recommendations From the International Stroke Genetics Consortium, Part 2: Biological Sample Collection and Storage

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on behalf of the International Stroke Genetics Consortium

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