PROTOCOL

TITLE:	**A Single-Site Tissue Repository Providing Annotated Biospecimens for Approved Investigator-directed Biomedical Research Initiatives**
PROTOCOL NUMBER:	SAN-BB-02
PRINCIPAL INVESTIGATOR:	Houman Hemmati, M.D., Ph.D.
SPONSOR:	Sanguine Biosciences, Inc. 318 Bear Hill Road, Suite 1 Waltham, MA 02451
VERSION:	1.0
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PROTOCOL SIGNATURE PAGE

Statement of Compliance:

The trial will be conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP), and all applicable laws and regulations including the following United States Code of Federal Regulations (CFR). The CFR's applicable to clinical studies (§ 45 CFR Part 46, § 21 CFR Part 50, and § 21 CFR Part 56).

As Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participant. All personnel involved in the conduct of this study have completed human subject protection and ICH GCP training.

The protocol, informed consent form(s) (ICFs), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form is obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who have already provided consent, using a previously approved consent form.

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Investigator Signature: _____ Date: _____

Investigator Print Name: _____

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1 PROTOCOL SYNOPSIS

SPONSOR: Sanguine Biosciences, Inc.

STUDY TITLE:

A Single-Site Tissue Repository Providing Annotated Biospecimens for Approved Investigator-directed Biomedical Research Initiatives

PROTOCOL NUMBER: SAN-BB-02

PRIMARY OBJECTIVE:

To collect, preserve, and/or distribute annotated biospecimens and associated medical data to institutionally approved, investigator-directed biomedical research to discover and develop new treatments, diagnostics, and preventative methods for specific and complex conditions.

STUDY DESIGN:

- A single-site, cross-sectional study
- Biological tissue samples will be collected from study participants, processed, and preserved in the biorepository's cryogenic core biobank (hereinafter, "biobank") until a research study requests a sample.
- If a sample does not require processing, the sample may be delivered directly to the requesting researchers or designated third parties.
- Health information will be collected via self-report and medical record review to obtain a detailed clinical history of the participant'shealth. This information includes but is not limited to demographic and lifestyle information, current medications and comorbidities, date of diagnosis, condition-related treatment history, current disease characteristics, diagnostic reports, and family medical history.
- Sanguine will implement a software-as-a-service (SaaS) provider of electronic signature technology and transaction management solutions or a hardcopy of the informed consent form (ICF). Participants may electronically sign the ICF and authorization of release of information using an electronic device. The Sponsor may alternatively provide the participant the option of completing hardcopy documents if they so desire. In addition to the Principal Investigator (PI), approved study staff can also administer and sign the ICF and will address all of the participant's queries regarding the ICF and study design.
- All participants biospecimens, if processed, will be stored and distributed by blinded personnel to the participants direct identifiers.

DURATION OF PARTICIPANT PARTICIPATION:

- This study requires the collection of a tissue sample, which is considered active participation. Study enrollment and the sample collection take about one hour or more to complete depending on the number and types of samples collected. Therefore, active participation will be about one hour and may be up to two hours.
- Inactive participation lasts as long as a participants samples and data remain at the biobank. There is no limit on the length of time samples and data may be stored. The samples may remain indefinitely at the biobank or until the participant decides to withdraw their participation from the study.

STUDY POPULATIONS:

Health Condition Group:

Health Condition Group Inclusion Criteria:

- Persons 18 to 85 years of age at the date of informed consent.
- If presenting with a history of a specific condition, the diagnosis is confirmable in the medical record or may be confirmed using other forms of verification including self-reporting.
- Understands the procedures and requirements of the study by providing written informed consent (or verbal assent if a legally authorized representative will sign the ICF), including consent for authorization for protected health information disclosure.

Health Condition Group Exclusion Criteria:

- Persons younger than 18 years of age or older than 85 years of age at the date of informed consent.
- Receipt of blood products 30 days before the study blood draw.
- Receipt of an investigational (unapproved) drug 30 days before the study blood draw.
- A confirmable diagnosis of any medical condition that would increase potential phlebotomy risks. Such medical conditions include:
    - Severe or untreated cardiovascular diseases;
    - Bleeding disorders;
    - Late-stage chronic kidney disease; and/or
    - Conditions associated with chronic anemia.
    - Stage 3 and 4 cancers
- Pregnancy
- Has donated a unit of blood within the last 2 months at the date of informed consent.

Exceptive Condition Group:

Exceptive Condition Group Inclusion Criteria:

- Persons 18 to 85 years of age at the date of informed consent
- If presenting with a history of a specific condition, the diagnosis is confirmable in the medical record.
- A confirmable diagnosis of any medical condition that would increase potential phlebotomy risks. Such medical conditions include:
    - Severe or untreated cardiovascular diseases; (including a stroke or myocardial infraction within the last 2 months)
    - Bleeding disorders;
    - Late-stage chronic kidney disease;
    - Splenomegaly;
    - Pregnancy; and/or
    - Conditions associated with chronic anemia.
- Understands the procedures and requirements of the study by providing written informed consent (or verbal assent if a legally authorized representative will sign the ICF), including consent for authorization for protected health information disclosure.

Exceptive Condition Group Exclusion Criteria:

- Persons younger than 18 years of age or older than 85 years of age at the date of informed consent.
- Receipt of blood products 30 days before the study blood draw.
- Receipt of an investigational (unapproved) drug 30 days before the study blood draw.
- Has donated a unit of blood within the last 2 months at the date of informed consent.

Control Group:

Control Group Inclusion Criteria:

- Persons 18 to 85 years of age at the date of informed consent.
- Understands the procedures and requirements of the study by providing written informed consent (or verbal assent if a legally authorized representative will sign the ICF), including consent for authorization for protected health information disclosure.

Control Group Exclusion Criteria:

- Persons younger than 18 years of age or older than 85 years of age at the date of informed consent.
- Receipt of blood products 30 days before the study blood draw.
- Receipt of an investigational (unapproved) drug 30 days before the study blood draw.
- A confirmable diagnosis of any medical condition that would increase potential phlebotomy risks. Such medical conditions include:
    - Severe or untreated cardiovascular diseases;
    - Bleeding disorders;
    - Late-stage chronic kidney disease; and/or
    - Conditions associated with chronic anemia.
- Pregnancy
- Requires a Legally Authorized Representative (LAR) for the study informed consent.
- Has donated a unit of blood within the last 2 months at the date of informed consent.

STUDY OUTCOMES

The study's objective is to provide quality and standardized biospecimen collections to the biomedical community to facilitate future personalized medical care.

SAMPLE SIZE CONSIDERATIONS

The number of participants to be enrolled in this study is 20,000. The reason for 20,000 participants is that the Sponsor anticipates that over 2 years of the study, at least 50% of the participants will discontinue study participation. Because this study aims to establish a tissue biorepository for future therapeutic and diagnostic research endeavors, the Sponsor requires accrual and maintenance of a large enough biospecimen cohort for research clients to obtain statistically significant results. Therefore, the Sponsor believes that this sample size will provide the required sample diversity and volume to achieve statistically significant results despite participation attrition.

2 BACKGROUND & RATIONALE

To collect, preserve, and/or distribute annotated biospecimens and associated medical data to institutionally approved, investigator-directed biomedical research to discover and develop new treatments, diagnostics, and preventative methods for specific and complex conditions.

Biomedical research has utilized biorepository specimens for decades. Starting as small, private tissue collections, investigators analyzed small cohorts of samples to validate an anticipated molecular or genetic aberration specific to a particular disease. In recent years, advances in molecular and genetic research techniques have extended the ceiling of biomedical research potential allowing large volumes of samples, genes, and molecules surrounding a disease to be analyzed quickly and cost-effectively.[1] One major factor now governing translational research is the availability of quality biospecimens to deliver quality results.

The National Cancer Institute surveyed over 700 investigators regarding their research experience with biobank specimens. Over 60% of researchers surveyed considered the specimens to be under-annotated, 47% stated the quality was questionable.[2] This led to 60% of researchers questioning their findings and over 80% were forced to limit the scope of their proposed research.[2] It is evident that the quality of research conducted using biobank specimens would be greatly enhanced by standardized collection and storage processes assuring the uniform quality of the material to be studied.

Another factor hindering the clinical applicability and impact of biomedical research findings is the limited volume and diversity of available samples for analysis. Traditional institutionally established biobank collections are restricted by regional location and the population.[3] Such biobanks are also limited to collect specimens from people seeking medical care.[3] Analyzing molecular patterns present within these collections limits the applicability of investigational findings.

A third issue limiting the scope of current molecular and genetic research methods is the sheer complexity of health conditions, both etymologically and in terms of therapeutic efficacy. Researchers have exhausted the effects of one to a few genes on a disease state. When mutated, a single gene can trigger a rare inherited disorder such as Huntington's disease, which is an increasingly infrequent discovery. Many diseases are increasingly viewed as complex conditions affected by numerous genes of varying influence. In oncology alone, there are more than 100 known types of cancer, mostly named after the organs they were first located and the type of cells from which they originate.[4] Yet, these common pathological designations are rapidly becoming less definitive as molecular markers become more clinically relevant in the era of personalized medicine. The National Comprehensive Cancer Network (NCCN) has more than forty molecular biomarkers for clinical practice to characterize six of the most common types of malignancies.[5] The NCCN has designated an entire task force to vet the increasing number of potential markers for clinical use.

Molecular markers can be diagnostic, prognostic, or predictive and are revolutionizing cancer treatment through the elucidation of genetic factors, which can influence a participant's specific therapeutic course. Cancer is comprised of hundreds of distinct molecular diseases. The ability to molecularly distinguish cancer types independent of routine gross and microscopic inspection holds the potential for discovering therapeutic similarities between well-documented and

uncommon types of cancer. This may increase participant outcomes for rare forms of cancer. An example of this is imatinib; a drug approved by the FDA to treat leukemia. Researchers discovered molecular similarities between leukemia and gastrointestinal stromal tumors (GIST), making tumors responsive to imatinib.[6] This molecular correlation proved correct in clinical trials, and imatinib was FDA-approved to treat GIST.

Cancer is one of many fields exploring genetic and molecular variability between disease subtypes and individuals. Autoimmune, metabolic, cardiovascular, and most other common and rare health conditions are influenced by genetic predisposition and environmental and comorbid factors.[7] Common conditions such as atherosclerosis or diabetes mellitus are caused by deficiencies in multiple genes combined with diet or lifestyle habits. Because each gene contributes a small amount to overall risk, varying signals are emitted, confounding efforts to associate it with a specific disease state. Therefore, researchers need to study the genetic profiles of many people, incorporating phenotypic and health data to maximize clinical impact. In addition to the molecular complexity of the pathophysiology of health conditions, treating diseases can be just as complex. It is well known that standards of treatment do not consistently work from participant to participant. Therefore, to more effectively treat participants, physicians must understand the genetic complexity associated with certain medical conditions and the individual. To decipher the genetic web that governs certain conditions, researchers must study a large and diverse cohort of genetic material to arrive at statistically significant results.

2.2 Biomedical Research Methods and Diagnostic Markers

Biological research methods such as genetics and proteomics are beginning to develop a powerful influence in developing new medicines and diagnostics, which is an emerging area of biomarker development. Biomarkers are substances that can be found in the body when cancer is present. The classic tumor marker is a protein that can be found in the blood at increased levels when a certain type of cancer is present. Systemic Lupus Erythematosus can be detected from values of biomarkers present within a person's blood. In recent years, doctors have begun to develop newer types of biomarkers using different types of biological and genetic material. Bioinformaticians and molecular biologists have deemed this field of biomarker discovery using the suffix "*omics*." Examples of *omics* include *genomics, proteomics, metabolomics,* and *pharmacogenomics*.

The study of patterns of DNA changes (or mutations) is called *genomics*.[8] We know that most health conditions have changes in DNA that direct the function of cells. By looking for DNA aberrations in blood samples, scientists may find complex genetic patterns that characterized certain health conditions. *Pharmacogenomics* analyzes an individual's response to certain drugs by looking at their genes.[8] Such analysis will help physicians choose the optimal treatment course for each participant maximizing drug efficacy while simultaneously minimizing adverse effects, truly personalizing medicine.

Another approach, called *proteomics*, looks at the patterns of all the proteins in the blood instead of looking at individual protein levels.[9] New testing equipment allows researchers to look at thousands of proteins at one time. It is unlikely that such a test would be used in the clinic, but it may help researchers narrow down which protein levels are important in a certain disease state. This information could then be used to develop a diagnostic test looking only at these important proteins. Alternatively, treatment may be developed to target these proteins affecting the

pathophysiology of a condition or to test the efficacy of a certain therapy used in a case. These new testing methods are still in the early stages of development. Very few are in routine use at this time.

Metabolomics studies the chemicals and molecules created during specific cellular processes (metabolites).[10] Metabolomic profiles can capture a cell's physiology at a specific time. Metabolites are much smaller than proteins. Therefore, *metabolomics* allows researchers to view a broader range of chemicals within the molecular spectrum.[10] Working together with *proteomics*, researchers can put together a complete picture of cellular pathways utilized by health conditions.

The *omics* field of biomarker discovery is but one new field currently explored by biomedical researchers. The concept of statistically analyzing a vast amount of data for patterns within whole populations is also an expanding area of interest for a couple of reasons. Such studies can be performed remotely on an electronic dataset by multiple investigators without depleting the physical biospecimen. Potential research studies for which Sanguine BioSciences, Inc., will provide biospecimens are not limited to the types of research discussed above. Instead, the purpose of the above discussion is to elucidate potential areas of future research to which biobank samples may be provided.

2.3 Study Rationale

The availability of high-quality biospecimens to use in such studies dictates the quality of scientific results achieved and remains a significant roadblock to the standardization of results in biomedical research. Following the accepted international best biorepository practices, Sanguine Biosciences, Inc. will provide superior biospecimen collection and processing to the research community. By following these practices, specimens will be a consistent grade to promote viable and reproducible scientific results. The primary purpose of SAN-BB-02 is to collect, preserve and/or distribute quality biospecimens with associated health data (annotations) to researchers. Not only will this study physically accomplish this task, but Sanguine Biosciences, Inc., will also establish an electronic DNA database. Through physical and electronic biospecimen collection, this study will create a shared research infrastructure for a large population of investigators, thus allowing them access to physical biospecimens, electronic genetic material, and associated health data. This dual method of biospecimen availability allows studies to fully explore their research initiatives with a direct emphasis on clinical impact.

Sanguine Biosciences, Inc., is a steward of health information, physical and electronic, biological and subjective, and provides a direct resource of molecular data for researchers via biological tissue collections and electronic genetic library. Sanguine BioSciences, Inc., will source potential participants using different public spheres to collect a diverse genetic and epigenetic cohort allowing for potential population-based investigations to discern general molecular trends in multifactorial conditions. Such wide-range studies can only be qualitatively accomplished by comparing a large condition-specific population against a diverse control population where biospecimen integrity is standardized across all samples. The core competency of this study is providing such samples to the research community to ensure quality results. Through valid population-based studies, personalized medicine can truly come into focus in the clinic. Individuals can be compared against molecular trends within a population to be diagnosed and treated according to molecular disposition instead of gross, histological, or clinical standards of

care currently in use.

3 STUDY OBJECTIVES & PURPOSE

The primary study objective is to collect, preserve, and/or distribute annotated biospecimens and associated medical data to institutionally approved, investigator-directed biomedical research to discover and develop new treatments, diagnostics, and preventative methods for specific and complex conditions.

To further study genotypic and phenotypic characteristics of specific and complex health conditions, the Sponsor may establish its biorepository to facilitate viable experimental results by supplying the research community with consistent, high-quality specimens. Sanguine BioSciences, Inc. (hereinafter, Sanguine) may collect biospecimens from health conditions participants and controls participants. Peripheral blood mononuclear cells (PBMC), serum, DNA/RNA, protein, and other blood portions may be extracted from blood samples and stored for future research. Other biospecimens that may be donated and stored include but are not limited to saliva, sputum, urine, hair, skin, nail clippings, stool, and semen. Demographically matched control samples may be collected to give researchers a baseline to compare against health condition samples. Control donors are considered participants who have not been clinically diagnosed with a medical condition.

Eventually, Sanguine may develop participant-derived induced pluripotent stem cells (iPS cells) to develop disease-specific cell lines that can be expanded in culture for research and development purposes only. The cells that we would obtain from participants blood do not divide in culture, and therefore will be available to a limited number of researchers. However, one can genetically transform those cells to divide. These cells are very similar to embryonic stem cells (cells that divide and transform into all types of cells – like nerve cells, skin cells, etc.)—allowing more of the participants cells to researchers working in specific conditions. The advantage of iPS cells – which are very similar to embryonic stem cells – is that they are not derived from human embryos, eliminating the ethical concern. By providing these samples to researchers, Sanguine will facilitate the pre-clinical analysis and correlation of genotypes with phenotypes (such as clinical outcomes).

The Sanguine biorepository may store biospecimens extracted from blood samples donated from control and health condition donors for unspecified future biological and biomedical research. The information gathered from this future research potentially include, but is not limited to:

- DNA/RNA/protein mutation analysis;
- DNA methylation analysis;
- Protein to DNA/RNA binding analysis; and/or
- Gene/protein expression analysis.

The additional information may help improve participant care by developing new diagnostics and therapies. The information will also help physicians understand how and why specific treatments behave differently in different participants, leading to individualized drug therapy for participants in the future.

Sanguine may also extend the biobank to include an electronic genetic database composed of

partial and whole sequences of the participants DNA and RNA. Such a library would allow more researchers to utilize the biobank samples than possible through traditional physical biobanking means.

4 STUDY DESIGN

4.1 Study Design Rationale

Researchers with institutionally approved study initiatives may request and analyze the biospecimens, genetic material, and health data collected in this study to better understand specific health problems.

The information from this unspecified future biological and biomedical research may facilitate developing new diagnostic tools and personalized treatments for specific health conditions. Such conditions may be acute or chronic, specific or complex, prevalent or rare. Many health conditions overlap with each other clinically and genetically, necessitating in-depth molecular characterization of these conditions to diagnose and treat sufferers of such conditions successfully. Sanguine will facilitate these research endeavors by providing samples of standard quality collected during this study to research institutions.

The biobank may potentially collect biospecimens from rare populations such as elderly participants up to 85 years old. As the American population ages, the Sponsor feels that research on the aging process and conditions and diseases that disproportionately affect the elderly becomes increasingly important.

Other rare and underrepresented populations in research from which the study aims to collect include participants with infectious diseases, including, but not limited to, HIV/AIDS and hepatitis subjects. Because this is a potential population from which biospecimens may come, special training, consideration, and safety will be performed by study staff handling such specimens. Since it is considerably more dangerous to handle specimens with bloodborne pathogens present, many biorepository studies neglect to collect these populations. Unfairly neglected and under-represented within many biorepository cohorts, the Sanguine's biobank wishes to collect and store quality infectious specimens to help advance biomedical research of such diseases.

The study may require a tissue collection and/or a participant survey for participation. Most tissue collected will come from a blood draw; up to 100mL for the health condition group, 60mL for the exceptive condition group, and up to 180mL for the control group (if determined safe for the participant). Participant surveys may involve participant reported outcomes (PROs) or custom participant surveys.

Drawing up to 100mL for the health condition group will allow the biobank to collect enough blood from isolating several sub-products from the whole blood, such as serum, plasma, peripheral blood mononuclear cells (PBMCs), and genetic material (DNA/RNA), which are commonly used in biomedical research. A blood draw will provide biological tissue to research and expose participants to minimal risk.[11] A blood draw allows participants flexibility in scheduling the draw, either at a site or in the comfort of their home.

Due to a potential increase of phlebotomy risks for people with certain medical conditions such as cardiovascular diseases, bleeding disorders and late-stage kidney problems, the exceptive condition group will have only up to 60mL drawn to minimize these risks.

The study aims to collect biological tissue from multiple populations to support and advance biomedical research. Drawing a large volume of blood from healthy donors will provide more control biosamples for researchers (posing minimal risk to the participant). Allowing the study efforts to concentrate on collecting samples from various populations to service more research fields.

The control group may have up to 180mL of blood drawn for the study if determined that the participants health will not compromise their safety during the draw. The amount of 180mL is about one-third of the blood drawn during a blood donation and is considered by the Department of Health and Human Safety (HHS) to pose minimal risk to the participant. The study would like to have the potential to draw up to 180mL if the health of the participant allows this amount biological tissue to be collected from one appointment. Since the major risk and discomfort from venipuncture comes from being stuck with the needle, the study believes that a one-time blood draw of a larger volume would be potentially more comfortable for a healthy individual versus undergoing multiple venipunctures.

Participant health will be assessed prior to phlebotomy to determine maximum blood draw volume for all cohorts.

For all research requests that are not covered within this protocol, independent protocol amendments addressing the procedural changes may be drafted to address and minimize possible study risks. A medical practitioner will review the procedural amendments for safety assessment and submit to the IRB for review.

4.2 Description of the Study

This protocol is for a single-site, biospecimen collection study in adult participants. Participants will sign an informed consent (or provide verbal assent if a legally authorized representative will sign the consent) before the biospecimen collection(s). In addition to the Principal Investigator (PI), trained study staff (e.g., research coordinators,and phlebotomists) can screen a potential participant to determine their study eligibility and can administer and sign the Informed Consent Form (ICF) with the participant and address all of their questions regarding the ICF and study design.

As a next step, a research coordinator will set up a potential enrollment appointment with a contracted mobile phlebotomist. Health condition, exceptive condition, and control participants will be recruited by one or any of the following resources, but not limited to:

- Use of online marketing where potential participants receive study information from the Sanguine's website or online participant referral program;
- In the site investigators (or PI's) clinic; and/or
- Through community advocacy programs.
- Participant Referral

In all cases, potential participants will not be contacted by Sanguine study staff before agreeing to Sanguine's Privacy Policy, available online, or by contacting Sanguine directly via phone or email.

Participants who have agreed to participate and who have signed the ICF for Study SAN-BB-02 (or given assent if a legally authorized representative will sign the ICF) will be eligible to

participate in this biorepository study. A signed ICF will be obtained from those participants who choose to participate. After obtaining the informed consent for this study, a professional phlebotomist, nurse practitioner, physician, or other qualified health professional will collect specified tissue samples. Blood samples will be drawn, and minimal risk tissue collection procedures may be performed at the participant's home, workplace (in a private setting), other private settings, or selected clinics.

Blood samples, serum, plasma, PBMCs, and other blood portions may be processed. Additionally, DNA and/or RNA may be extracted from the collected blood samples by Sanguine. Other biospecimens that may be donated will be stored in whole or delivered directly to requesting researchers and/or designated third parties. Biospecimens will be stored in Sanguine's biobank indefinitely or until they are exhausted.

The participant's biospecimens will be annotated with self-report or medical review health information. The biospecimens and the linked clinical data will be de-identified. End users will not have any access to unique participant identifiers.

Participants may be asked to complete a participant survey either in tandem with the biospecimen collections or following a separate, variable schedule that can be customized depending on need.

4.3 Compliance with Laws and Regulations

This study will be conducted in accordance with applicable U.S. Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) regulations, the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws. The Sponsor is responsible for personnel regulatory education in standard operating procedures and educational materials and training. The Office of Human Research Protection (OHRP) provides guidance on ethical and regulatory issues encountered in biomedical human participant's research. Sanguine strives to adhere to OHRP guidelines and compliance with DHHS Code of Federal Regulations (CFR) Title 45, Part 46 (45 CFR 46).

Laboratory compliance is consistent with national good laboratory practices and follows the International Society of Biological and Environmental Repositories (ISBER) best practice.

5 STUDY METHODS

5.1 Sample Size

The number of participants to be enrolled in this study is 20,000. The reason for 20,000 participants is that the Sponsor anticipates that over2 years of the study, at least 50% of the participants will discontinue study participation. Because this study aims to establish a tissue biorepository for future therapeutic and diagnostic research endeavors, the Sponsor requires accrual and maintenance of a large enough biospecimen cohort for research clients to obtain statistically significant results. Therefore, the Sponsor believes that this sample size will provide the required sample diversity and volume to achieve statistically significant results despite participation attrition.

Sanguine anticipates collecting biospecimens not only from participants with known health conditions but also from control participants with no known health conditions. These control biospecimens may be requested for comparison against other condition-specific biospecimens stored in the biobank. The total population of control participants is undetermined but will be included in the 20,000 total study participants.

5.2 Participation Criteria

Eligibility and applicable participant medical history will be overseen by a medical doctor throughout the course of the study to assess participant safety. About 85% of research requests can be completed by the protocol procedures, herein. Some research requests cannot be fulfilled using the procedures discussed below. These requests will be submitted to the IRB as an amendment to this protocol. A medical doctor will review these exceptional collection requests to assess participant safety.

5.2.1 Health Condition Group

Health Condition Group Inclusion Criteria:

- Persons 18 to 85 years of age at the date of informed consent.
- If presenting with a history of a specific condition, the diagnosis is confirmable in the medical record.
- Understands the procedures and requirements of the study by providing written informed consent (or verbal assent if a legally authorized representative will sign the ICF), including consent for authorization for protected health information disclosure.

Health Condition Group Exclusion Criteria:

- Persons younger than 18 years of age or older than 85 years of age at the date of informed consent.
- Receipt of blood products 30 days before the study blood draw.
- Receipt of an investigational (unapproved) drug 30 days before the study blood draw.
- A confirmable disease of any medical condition that would increase potential phlebotomy risks. Such medical conditions include:
    - Severe or untreated cardiovascular diseases;
    - Bleeding disorders;
    - Late-stage chronic kidney disease; and/or
    - Conditions associated with chronic anemia.
- Pregnancy
- Has donated a unit of blood within the last 2 months at the date of informed consent.

5.2.2 Exceptive Condition Group

Exceptive Condition Group Inclusion Criteria:

- Persons 18 to 85 years of age at the date of informed consent

- If presenting with a history of a specific condition, the diagnosis is confirmable in the medical record.

- A confirmable diagnosis of any medical condition that would increase potential phlebotomy risks. Such medical conditions include:
    - Severe or untreated cardiovascular diseases (including a stroke or myocardial
    - infraction within the last 2 months)
    - Bleeding disorders;
    - Late-stage chronic kidney disease;
    - Splenomegaly;
    - Pregnancy; and/or
    - Conditions associated with chronic anemia.
- Understands the procedures and requirements of the study by providing written informed consent (or verbal assent if a legally authorized representative will sign the ICF), including consent for authorization for protected health information disclosure.

Exceptive Condition Group Exclusion Criteria:

- Persons younger than 18 years of age or older than 85 years of age at the date of informed consent.
- Receipt of blood products 30 days before the study blood draw.
- Receipt of an investigational (unapproved) drug 30 days before the study blood draw.
- Has donated a unit of blood within the last 2 months at the date of informed consent.

5.2.3 Control Group

Control Group Inclusion Criteria:

- Persons 18 to 85 years of age at the date of informed consent.
- Understands the procedures and requirements of the study by providing written informed consent (or verbal assent if a legally authorized representative will sign the ICF), including consent for authorization for protected health information disclosure.

Control Group Exclusion Criteria:

- Persons younger than 18 years of age or older than 85 years of age at the date of informed consent.
- Receipt of blood products 30 days before the study blood draw.
- Receipt of an investigational (unapproved) drug 30 days before the study blood draw.
- A confirmable diagnosis of any medical condition that would increase potential phlebotomy risks. Such medical conditions include:
    - Severe or untreated cardiovascular diseases

- Bleeding disorders;
- Late-stage chronic kidney disease; and/or
- Conditions associated with chronic anemia.

- Pregnancy
- Requires a Legally Authorized Representative (LAR) for the study informed consent.
- Has donated a unit of blood within the months at the date of informed consent.

5.3 Participant Procedures

The components of this study include:

1. Participant recruitment
2. Pre-consent Inclusion/Exclusion Screening
    a. Collection of demographic data
    b. Collection of self-report health history
3. Cohort Placement
    a. Health Condition Group
    b. Exceptive Condition Group
    c. Control Group
4. Study enrollment and Informed Consent process
5. Biospecimen Collection
    a. Blood draw by a certified medical professional. Medical history considered.
    b. Minimal risk biospecimen collection
    c. Biospecimens that require a clinical procedure and are considered more than minimal risk
        i. Participant signs procedure-specific ICF
        ii. Procedures performed by trained medical professionals such as physicians and nurses and at study-approved sites
6. Participant surveys, questionnaires, and PROs
7. Recovery time assessment by the study staff depending on the type of specimen collected, medical history, and health of the individual.
8. Data is securely stored through electronic and physical means.

Please see Appendix C for participant safety workflow.

5.3.1 Recruitment

Participants may be recruited through identification by a study site investigator (e.g, PI) verbal referral by study participants, web-based media, or community advocacy events.

Potential participants must consent to be contacted either by opting in to the Privacy Policy online or contacting Sanguine directly via email or phone. The signup process captures direct participant identifiers such as:

- Name
- Email address

- Telephone number
- Residential address
- Date of birth
- Sex
- Ethnicity
- Have you been diagnosed with a medical condition? Yes/No
- Have you participated in a clinical trial in the past 30 days? Yes/No

By submitting this information, a health profile is generated within Sanguine's database. This information is securely captured, and a research coordinator will contact the potential participant for the next steps in study participation. The initial contact call will consist of an introduction to the study and inclusion/exclusion evaluation. The screening process is described in more detail in section 4.3.2.

5.3.1.1 Online Recruitment

Participants may be recruited online through patient advocacy websites, social websites such as Craigslist, Sanguine Bioscience's Facebook page, and Sanguine's website. The Sanguine website provides information to potential participants about the Sanguine biobank through its website, explaining study objectives and participation requirements. Participants may also receive updates regarding condition-specific current active biospecimen collections.

Participants can also refer friends and family to participate in the biobank study. Current participants can enroll on Sanguine's website. The referral recruitment method is initiated and controlled solely by study participants.

All potential participants recruited/referred to Sanguine's biobank study must consent to be contacted, permitting study staff to contact them. Through the successful completion of study procedures and referral, participants may be awarded points.

5.3.2 Potential Participant Inclusion/Exclusion Screening

From the screening process, study staff will determine if the potential participant can enroll in the study or not. After the potential participant has signed up, a study staff member will contact the potential participant to introduce the study and evaluate participant inclusion/exclusion. During this process, direct participant identifiers will be collected. Data collected include but are not limited to a physical address, date of birth, and general medical history associated with a specific condition. Please see Appendix D for an example of medical information collected.

5.3.3 Potential Participant Cohort Placement

After the screening process, trained study staff will review the self-reported medical history to determine cohort placement. If the participant does not report any medical conditions or remarkable medical history, they will be placed in the control cohort. If the participant has reported a medical condition that could potentially increase the presentation of risks associated with phlebotomy, such as bleeding disorders, severe or untreated cardiovascular diseases, late-stage chronic kidney diseases, pregnancy, or splenomegaly, the participant will be placed in the exceptive condition cohort. This cohort identification is designed to distinguish participants who require additional protection during a phlebotomy procedure. All other participants will be placed

in the health condition group. If a participant does not meet inclusion/exclusion criteria, they will be notified that they cannot participate in this study.

5.3.4 Informed Consent

The informed consent process will occur either at the Sponsor site or in the comfort of the participant's home, where trained study staff will explain the ICF, study design, participation requirements, and reasonable risks. Participants will be encouraged to ask questions regarding the ICF, study design, and what is being asked of them. The study staff will assess the participants understanding of the entire informed consent, including but not limited to the voluntary nature of study participation, their ability to withdraw from the study at any time, and participation requirements. After signing the ICF, participants will get a copy of the signed ICF for their records.

If the participant is unable to give informed consent, a legally authorized representative (LAR) may sign the ICF, in addition to the participant's verbal assent. Trained study staff will decide whether a LAR may or may not be used.

Participants requiring LARs include but are not limited to participants with mental health disorders, genetic disorders such as Huntington's disease, and neurological conditions such as Alzheimer's disease.

For this study, a legally authorized representative may include:

1. An agent pursuant to an advanced health care directive;
2. A spouse, or
3. A child having the authority to make health care decisions. When possible, the participant will be involved in the informed consent process and provide assent to the best of their ability.

Since Sanguine acts as a Sponsor and as a site, there will be two scenarios for participant consenting and data transfer:

1. As a site, Sanguine will implement a software-as-a-service (SaaS) provider of electronic signature technology and transaction management solutions, so participants electronically sign the ICF and authorize the release of medical records using a tablet or computer from the comfort of their home or through a secure website.
2. Alternatively, if the participant prefers, physical ICFs and information release authorization may be completed using hardcopy documents.

5.3.5 Biospecimen Collection

Biospecimen collection will occur either at a study-approved clinic, in the comfort of the participant's home, at the participant's workplace (in a private setting), or in other private settings. Participation requires at least one type of tissue collection described below. Biospecimens are collected as a donative gift from the participant to the Sponsor.

5.3.5.1 Blood Collection

A blood draw is the most common type of biospecimen collection procedure, making up about

95% of biospecimen requests. Blood will generally be collected by venipuncture from a medical professional certified in phlebotomy. Participants may also be asked to provide a microsample of blood via fingerstick. Fingerstick samples will be collected on a blood card, such as a dried blood spot (DBS) card, or into a microtainer. Researchers may use the blood cards for specific testing of biomarkers or isolating genetic material.

Blood collection volumes are dependent on which cohort the participant is placed and self-reported medical data (see Table 1). Blood may be collected every 7 days, but the total volume collected during a 6-week period may not exceed the Table 1 volumes. Maximum blood collection volumes in Table 1 may be collected at one time

Table 1: Maximum Blood Collection Volume by Cohort

Cohort	Blood Draw Volume (mL)
Health Condition	≤100mL
Exceptive Condition	≤60mL
Control	≤180mL

The maximum blood collection volume within a 6-week period by cohort.

Participants within the health condition and control groups who weigh less than 110 pounds and/or are older than 85 years old will have a maximum collection volume of 75mL within a 6-week period.

Before the phlebotomy procedure, a Sanguine designated phlebotomist will assess the participants health by asking questions like, “Do you feel healthy today?” and noting any physical symptoms that may require the blood draw to be aborted. The phlebotomist then decides if the blood draw can continue as scheduled. The blood draw appointment follows phlebotomy best practices set forth by the College of American Pathology (CAP) and the World Health Organization (WHO). Venipuncture is attempted no more than 3 times. After a third failed attempt, the blood draw is canceled. After the blood draw, the phlebotomist will remain with the participant until the wound has successfully clotted and/or the participant reports that they feel well enough to resume light activities.

5.3.6 Control Group

Each participant’s health history will be collected before the blood draw to determine the health and safety of each participant during the venipuncture procedure. The participant’s self-reported medical history is reviewed by trained study staff to assess any medical history that would place a participant at increased risk during a blood collection.

If the participant qualifies for the control group and a researcher has requested the maximum blood volume to be collected, the study staff must assess the health of the participant to determine if they are healthy enough to undergo a 180mL blood draw. The following questions are asked to the participant to assess the s safety during the 180mL blood draw:

Must answer “YES” to all questions in order to be considered for 180mL draw

1. Is the participant's weight ≥110lbs?
2. Is the participant younger than 85 years old?
3. Does the participant have difficulties with blood draws (e.g., hard stick)?

5.3.7 Optional Biospecimen Collection

Participants may be asked to donate other biospecimens such as saliva, stool, urine, sputum, semen, hair, nail clippings, skin cells from a skin or swab or skin taping strips, cells from the mouth via buccal swab, and respiratory mucosa or nasal samples from a nasal or nasopharyngeal swab. The collection methods of these biospecimens are considered no more than minimal risk to the participant.

Participant facing visit guides may be created for any required self-collections. This documentation will be approved by the IRB for approval prior to any applicable collection taking place.

5.3.8 Participant surveys, questionnaires, and PROs

Participants may be asked to complete a survey, questionnaire, or PRO, either in conjunction with a biospecimen collection or following a separate, variable schedule.

Sanguine sends a single question, non-study specific survey to participants post-screen, and post-scheduled appointment for feedback on their experience.

5.3.9 Recovery Time

Depending on how much blood is drawn, pertinent health history (including current medications), and other tissue donation procedures performed, the phlebotomist and/or study staff will determine how much time a participant will need to recover from the procedure. Steps to recovery include hydration, a snack, and a period of rest before performing strenuous activities or heavy lifting. Phlebotomists will remain with the participant after the phlebotomy procedure to ensure proper clotting and the participant feels well-enough to perform daily activities.

After the visit is completed, Sanguine will send a post-visit survey to the participants for feedback on their experience. Refer to Appendix D for a survey example.

5.3.10 Collection of Protected Health Information (PHI)

Participants will have their protected health information collected in two ways: self-reported data and a thorough review of their medical records. Upon enrollment, participants will be asked to authorize the release of their health information. Participants who deny this authorization may affect their enrollment within the biobank study. Upon receiving this authorization, study staff will request medical data from the appointed healthcare provider. This data will be secured by physical, electronic, and administrative means.

The biobank has security measures to protect the participant's PHI and are discussed in Section 6 and Section 7.

5.4 Confidentiality/De-identification Process

The research on the biospecimens will be performed without the use of the participant's names, pictures, address, or any government-issued identification numbers (such as social security number) or any other direct identifiers as stated in the Health Insurance Portability and Accountability Act (HIPAA). Participants will be randomly assigned a unique participant identifier. This number will be used to identify the participant on all documents.

5.5 Direct Access to Source Data/Documents

The investigator and/or institutions involved in this study will agree to allow trained employees from Sanguine direct access to all source data and documents, including the participants complete medical records. Access must also be granted to authorized auditors, IRB reviewers, and all applicable regulatory bodies, as necessary.

5.6 Sample Processing and Storage

Sanguine follows the International Society for Biological and Environmental Repositories (ISBER) and NCI repository best practices to assure quality biospecimen processing and storage. Guidelines for these best practices have been adapted to Sanguine's specific laboratory space and personnel and are specified in applicable lab procedures. In accordance with these guidelines and to assure quality, each type of biospecimen extracted and processed on behalf of the Sponsor follows a specific standard operating procedure.

Biospecimens extracted and processed by Sanguine for storage and redistribution to researchers include, but are not limited to, serum, plasma, PMBC's, DNA, and RNA. Biospecimens are stored in cryogenic containers. To control biospecimen quality the cryogenic containers are constantly monitored for temperature oscillations, which are recorded electronically. In the future, the biobank may store dehydrated samples at ambient temperature as approved and accepted by biorepository storage practices. As a part of the biorepository protocol, specimens will remain at Sanguine indefinitely or until they are distributed to an approved research study.

Detailed sample collection and shipping documentation will be provided to each site by Sanguine. Samples collected may be shipped overnight directly to the requesting researcher and/or designated third party, dropped off same-day to the requesting researcher, or shipped overnight to one of Sanguine's processing labs. Shipments may be frozen, ambient, or refrigerated. The lab verifies incoming samples before processing begins. All direct participant identifiers are blinded to the laboratory staff and researchers. Parent samples will be labeled with the unique participant identifier, as specified in the applicable lab procedures.

All procedures for collecting, handling, storing, and shipping biobank materials are specified in the biorepository standard operating procedures or specific study documentation. Sanguine follows the International Society for Biological and Environmental Repositories (ISBER) and NCI repository best practices to assure quality biospecimen processing and storage.

5.7 Biospecimen & Data Distribution Procedures

Sanguine will provide quality biospecimens to institutionally approved pre-clinical and clinical investigator-led studies for diagnostic, therapeutic, and preventative research. Once the Sponsor receives an order for biospecimens and associated clinical records from a client, the Sponsor will

ship the requested biospecimens at either room temperature, refrigerated, or cryogenically to the client. The Sponsor will deliver the associated, redacted health information to the client either electronically or physically. Third parties receiving annotated biospecimens or access to the electronic biospecimen library must agree to Sanguine's terms and conditions and/or complete a Materials Transfer Agreement to minimize risks associated with the transfer of biospecimens and health information. Third parties must agree to use biospecimens for research purposes as specified in the informed consent and agree not to seek out the identity of participants.

The Sponsor will also provide potential client investigators with access to available de-identified biospecimens and clinical information (de-identified DNA sequences and associated de-identified electronic medical records and participants' self-reported but de-identified information) through a data tracking application.

●

5.8 Study Termination

Participants will be considered inactively involved in SAN-BB-02 indefinitely or for as long as their biospecimens and data remain stored within the biobank. A participants participation may be terminated partially or completely.

Guidelines for these best practices have been adapted to Sanguine's laboratory partners and personnel and are specified in Sanguine's SOPs.

5.9 Participant-Initiated Withdrawal

Participants have the right to withdraw from the study at any time. There is no penalty if the participant decides to end his/her participation. For a participant to withdraw from the study, a written or verbal request must be made to Sanguine's study staff. Participants do not need to give a reason for changing their minds. Biospecimens and health data may be handled after withdrawal in two ways:

1. **No Longer Interested.** The study no longer has contact with the participant, and the authorization for the release of information expires. The biobank still has permission to use all biospecimens and data stored within the biobank at the time of withdrawal.
2. **No Longer Interested - Destroy Remaining Samples/Data.** The study no longer has contact with the participant, and the authorization for the release of information expires. All samples and data remaining in the biobank are destroyed.

If it is not clear how the participant wants the samples and information handled from your written request, the Sponsor will treat the withdrawal as "No Longer Interested."

The biobank cannot recall samples and data that have already been given to third-party researchers.

5.10 Investigator-Initiated Withdrawal

The site investigator or Sponsor may remove a participant from the study at any time and for any reason. Since the biobank does not provide medical treatment or health care, there will be no penalty imposed upon the participant. Reasons for which the PI or site investigator may terminate a participant's enrollment may include but are not limited to: the participant does not follow study directions, or the Sponsor stops the study for any reason.

6 RISK/BENEFIT ASSESSMENT

6.1 Potential Risks

Potential risks associated with this study include physical and data-related risks.

Physical risks are those associated with venipuncture. At the time of the blood draw, the participant may experience a small amount of pain associated with introducing the needle into the skin, bruising at the venipuncture site, and a small risk of light-headedness or feeling faint, which are commonly associated with blood draws in general. There may also be slight discomfort or skin irritation due to hair sampling or skin taping.

This biorepository study is a study where biospecimens and associated medical data are stored indefinitely. Therefore, the main data-related risk is a breach of privacy. Though rare and unforeseen, a participant's private health information or identifiable information may become available outside the study. If a participant's insurance provider or employer becomes aware of the participant's study enrollment or experimental results associated with their specimens, the insurance provider or employer may participant the participant to health discrimination.

6.2 Risk Classification

The risk for the participant is minimal. There will be no additional discomfort to the participant beyond that ordinarily encountered during the performance of routine phlebotomy. Optional biospecimen donations are also considered a minimal risk and are collected via non-invasive means.

Some optional study procedures are considered more than minimal risk. If participation in such procedures is requested, an addendum to the ICF will be reviewed by the participant before the procedure is conducted. This addendum will describe all potential risks associated with these procedures.

6.3 Protection Against Risks

Physical risks associated with venipuncture will be minimized by utilizing experienced phlebotomists, nurse practitioners, or physicians to draw the blood samples. If the participant suffers a research-related injury, medical expenses will not be covered by the Sponsor. Study participants are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on those involved in the research.

All efforts will be made to minimize data-related risks through several levels of protection. First, potential participants are made aware of the potential risks outlined within the ICF during the informed consent process. At the time of potential participant s consent to be contacted either by opting in to the Privacy Policy online or contacting Sanguine directly via email or phone, the participant is given a unique participant identifier, which does not utilize any of his/her direct identifiers (e.g., birth date, zip code, or social security number) as outlined in HIPAA. So, the participant is identified within the study only by this study ID. Biospecimens are processed and stored with sample-specific identification, which is electronically linked to the study ID. Therefore, only necessary study personnel are exposed to the study ID that cannot be connected

with the participant's direct identifiers unless one has administrative access to the linking list portion of the database. Sanguine is guided by the 45 CFR 160 and 164, also known as the Security Rule within HIPAA, to protect participants' privacy and confidential information.

Sanguine uses honest brokers to collect linking information of participants with study identifiers. Such honest brokers are participant to privacy policies and procedures created by Sanguine that adhere to applicable privacy regulations. Access to participant identifiers is physically restricted via password-protected levels within the study database. All physical private health identifiers are destroyed following HIPAA regulations. In addition, the study database is electronically monitored and records all information accessed by each study member. The study may seek a Certificate of Confidentiality (Certificate) to provide an extra layer of privacy protection to study participants. A Certificate may be sought by any research study that collects private health information and is awarded by the National Institute of Health (NIH) to protect human participant s in research against compulsory legal demands. It is possible participants diagnosed with an infectious disease may participate in the biobank. PHI protection for this population is considered of the utmost importance to discourage any potential health or social discrimination. All employees handling PHI will be trained regarding the importance of such sensitive information.

6.4 Potential Benefits

As a biorepository, this study aims to collect, store and distribute biospecimens for future research endeavors. Therefore, this study may not offer direct or immediate personal benefit to study participants. However, participant biospecimens utilized in future research may lead to new diagnostic and therapeutic techniques, which will benefit future participants with similar diseases.

7 ETHICAL CONSIDERATIONS

7.1 Online Recruitment

Participants can refer friends and family to Sanguine's IRB-approved studies through the Sponsor's website. The refer-a-friend recruitment method is initiated and controlled by participants. The Sponsor stores no contact information regarding third parties. Therefore, a third party voluntarily decides to contact Sanguine or not. Sanguine does store participant referral information and provides compensation for referrals. Sanguine personnel can contact potential participants only if the potential participant s provide consent to be contacted either by opting in to the Privacy Policy online or contacting Sanguine directly via email or phone. This policy highlights the participant's right to voluntary participation.

After a successful referral, Sanguine may make a monetary donation to the participant's nonprofit organization of choice. Sanguine's donation to nonprofit organizations on behalf of participants who successfully refer friends and family is innocuous. Since Sanguine's IRB-approved protocol does not provide treatment options for participants and is considered minimal risk, participants do not feel obligated or dependent upon the study or study staff for healthcare management. Therefore, such a donation would not be considered ethically negligent and does not create undue influence by the Sponsor.

7.2 Informed Consent Form

The IRB must approve the ICF and any other related documents prior to study initiation. The PI

or his/her designees must obtain a signed ICF for each participant and healthy donor participant. The Sponsor will retain the signed ICF. A copy of the signed ICF is given to each participant for their records.

The collection and blood processing/storing sites and the PI's Sponsor designees will comply with the study protocol and be responsible for the administration of the ICF and for acting in accord with HIPAA requirements. The biospecimens collection site is responsible for the accuracy and completeness of the data submitted and for making medical records and source documents available to the study Sponsor.

Sanguine research coordinators treat the informed consent as a process and not as a single event, carefully explaining all aspects of the study to each participant in language readily understood by the participant. The risks and benefits of participating in this study will be explained to each potential participant before entering the study. Participants will be made aware that their participation is entirely voluntary, and they may withdraw from the study at any time without penalty or repercussions. As a biorepository study, participants must understand their annotated samples will remain stored at Sanguine indefinitely or until a client requests them. In addition, the participant has the option of being re-contacted by the Sponsor to participate in other research studies. This preference is recorded on the ICF.

Sanguine or a designee is responsible for adequate training of the biospecimen collection site personnel and for monitoring these sites as required.

The Sponsor trains Sanguine research coordinators to explain and answer questions regarding the study to ensure the participant is fully informed about what is being asked of them.

The Sponsor allows study staff, directly and indirectly, involved with this biobank study and their family and friends to enroll and participate in the study. Since this study does not include any type of medical intervention or health care and active participation in the study is expected to be about one hour—or as long as it takes to complete the ICF process and the required biospecimen collection—undue influence or coercion of this population is minimal. All protected health information stored within the biobank database is treated with the same respect and care as all other participants. No unauthorized study staff may have access to this information, and employment status will not be influenced by information collected under this study as required by the Genetic Information Nondiscrimination Act (GINA).

7.3 Potential Collection from Participants with Infectious Diseases

People with infectious diseases are considered a vulnerable population for human participant's research because of multiple social, medical, and psychological issues. The biobank will consider these issues when recruiting and enrolling such participants. This study does not offer any medical intervention, and therefore, the Sponsor believes the risk of coercion or dependence upon the study staff will be minimal. The biobank's main risk is the privacy of all participants, and therefore, the privacy risks for participants with infectious diseases are already a top concern for the study.

7.4 De-identifying Protected Health Information Under the Privacy Rule and Disclosure of Data

Ethical issues of protection of privacy are the biobank's primary concern. The biorepository purpose is to supply the pre-clinical and clinical research community with quality biospecimens to promote therapeutic and diagnostic development. The repository provides well-characterized specimens annotated with relevant medical data derived from protected health information to facilitate good research. A prevailing concern regarding the inadvertent disclosure of such private information to employers or insurance providers exposes research participant s to potential discrimination. Health discrimination may include denial of healthcare coverage or even workplace retribution. Anonymizing samples would best protect participant s' identifying information but would severely limit the utility of experimental results. Therefore, to maximize study benefits and minimize participant risk, the Sponsor will make every effort to protect private health information.

Several laws are in effect to protect research participants and their privacy. GINA legally protects Americans from genetic discrimination, allowing them to pursue genetic testing for clinical or research purposes freely. This act is an important step to address the potential risks of storing genetic information. Still, research entities should look to themselves to ensure maximum efforts are applied to protect participant identifying information. To manage the information collected for sample annotation in the study database, the Sponsor has implemented a data breach notification system as specified in the Health Information Technology for Economic and Clinical Health (HITECH) Act. Sanguine adheres to the Office of Human Research Protection (ORHP) guidelines to best protect our study participants. Sanguine is also pursuing the award of an NIH Certificate of Confidentiality (Certificate) to further protect participant privacy from legal requests. A Certificate is a study-specific barrier to disclosure.

Health Insurance Portability and Accountability Act (HIPAA) defines policies and guidelines for maintaining participant privacy and confidentiality; specifically, the Security Rule outlines administrative, electronic, and physical barriers of protection against disclosure. Before seeking to release this health information to the Sponsor's clients, including clinical research organizations, research institutions, pharmaceutical, and biotechnology companies, the Sponsor must determine that the information no longer contains direct identifiers by removing specific pieces of information from each record that could directly identify a participant. Since the Sponsor does not participate in medical treatment or any therapeutic or diagnostic facet of healthcare, Sanguine is not considered a covered entity under the Privacy Rule. Therefore, Sanguine is not required by law to remove the 18 elements specified in HIPAA to comply with the Safe Harbor part of the Privacy Rule. The Sponsor does remove as many as possible to assure privacy protection while maintaining research relevance. The only one of the 18 elements the Sponsor currently does not redact is the treatment date to provide a complete health history to researchers.

7.5 Regulatory Compliance

This study will be conducted according to applicable requirements outlined in the FDA Code of Federal Regulations Title 21 and the ICH E6 Good Clinical Practice. The Sponsor is responsible for personnel regulatory education in standard operating procedures, educational materials, and training. ORHP provides guidance on ethical and regulatory issues encountered in biomedical human participant's research.

Sanguine strives to adhere to OHRP guidelines and is therefore compliant with the Health and

Human Services Code of Federal Regulations Title 45, Part 46 (45 CFR 46).

Laboratory compliance is consistent with national good laboratory practices and follows the International Society of Biological and Environmental Repositories (ISBER) best practices. Though the Sponsor site does not process tissue for clinical use, the Sanguine laboratory partner labs look to Clinical Laboratory Improvement Amendments (CLIA) for operations and quality standards guidance.

7.6 Principal Investigator

The PI, together with any designated sub-investigators, has the overall responsibility for the conduct and compliance of this biospecimens collection study according to this protocol and GCP.

8 RECORD RETENTION

Sanguine requires that all study-related documentation be retained and stored in Sanguine's database indefinitely.

9 FINANCIAL OBLIGATION & COMPENSATION

9.1 Financial Obligation of the Participants

The participant s will not incur any financial obligations.

9.2 Financial Compensation for Participation

The participants will be monetarily compensated, and Sanguine may also donate an equal amount on their behalf to a nonprofit organization of their choosing.

Although the research results, including donated biospecimens, may be patentable or have commercial value, the study participant will have no legal or financial interest in any commercial development resulting from the research.

10 INTELLECTUAL PROPERTY

All inventions and discoveries, including without limitation identification of markers and therapeutic drugs and all information and results from such discoveries, whether patentable or not, arising from this study or this protocol, shall be the property of the client investigator that procured associated samples and participant data from the Sponsor.

All rights, title, and interest in such discoveries and inventions, whether patentable or not, and all intellectual property rights therein shall be assigned to the client investigator that procured associated samples and participant data from the Sponsor.

All donated (remaining) samples are solely the property of Sanguine to be used solely in accordance with this protocol and the informed consent form.

11 APPENDIX A – WORKS CITED

WORKS CITED

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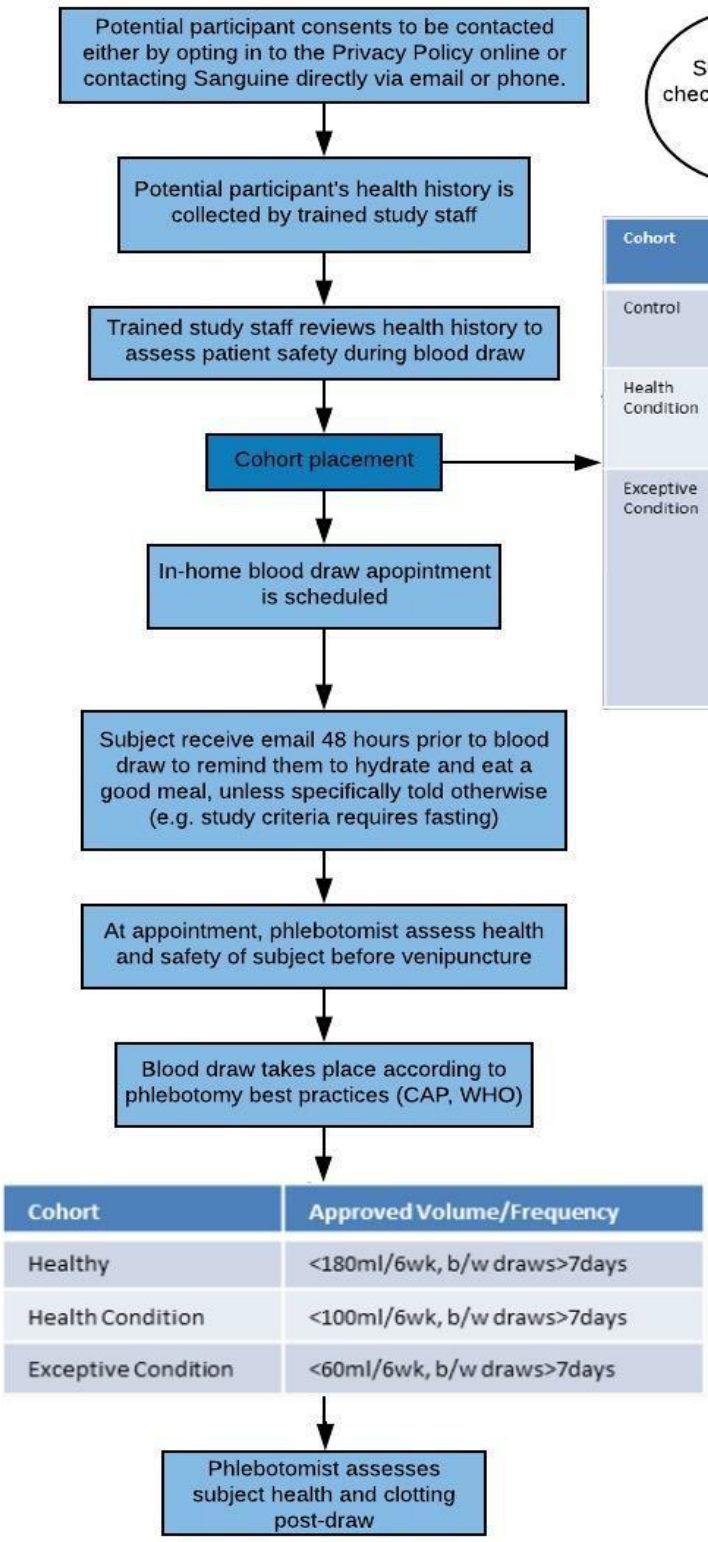
13 APPENDIX B – PARTICIPANT SAFETY PROCEDURE FLOW

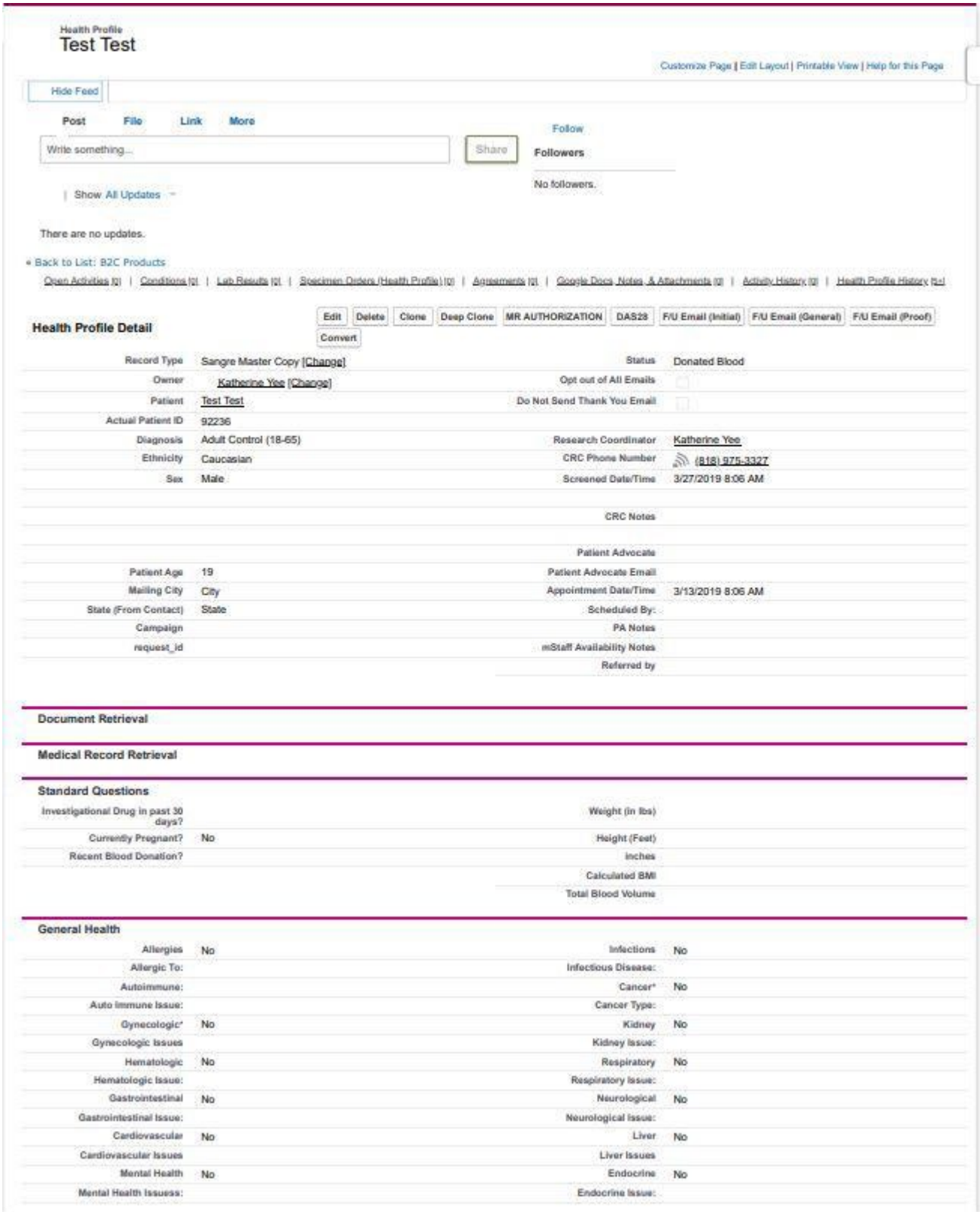


Subject health and safety is assessed multiple checkpoints to determine potential increased risk for study blood draw volume.

Cohort	Definition	Allowed Volume/Frequency
Control	No diagnosed medical condition	<180ml/6wk, b/w draws>7days
Health Condition	Diagnosed with medical condition (not considered "exceptive")	<100ml/6wk, b/w draws>7days
Exceptive Condition	Diagnosed with medical condition that may increase procedure risks associated with phlebotomy or cause or increase the chance of anemia (see protocol for examples)	<50ml/6wk, b/w draws>7days

Cohort	Approved Volume/Frequency
Healthy	<180ml/6wk, b/w draws>7days
Health Condition	<100ml/6wk, b/w draws>7days
Exceptive Condition	<60ml/6wk, b/w draws>7days

14 APPENDIX C – EXAMPLE OF DATA COLLECTED



Health Profile
Test Test

Customize Page | Edit Layout | Printable View | Help for this Page

Hide Feed

Post File Link More

Write something...

Share

Follow

Followers

No followers.

Show All Updates

There are no updates.

« Back to List: B2C Products

Open Activities (0) | Conditions (0) | Lab Results (0) | Specimen Orders (Health Profile) (0) | Agreements (0) | Google Docs, Notes, & Attachments (0) | Activity History (0) | Health Profile History (0)

Health Profile Detail

Edit | Delete | Clone | Deep Clone | MR AUTHORIZATION | DAS28 | F/U Email (Initial) | F/U Email (General) | F/U Email (Proof) | Convert

Record Type	Sangre Master Copy [Change]	Status	Donated Blood
Owner	Katherine Yee [Change]	Opt out of All Emails	
Patient	Test Test	Do Not Send Thank You Email	
Actual Patient ID	92236		
Diagnosis	Adult Control (18-65)	Research Coordinator	Katherine Yee
Ethnicity	Caucasian	CRC Phone Number	(818) 975-3327
Sex	Male	Screened Date/Time	3/27/2019 8:06 AM
		CRC Notes	
		Patient Advocate	
Patient Age	19	Patient Advocate Email	
Mailing City	City	Appointment Date/Time	3/13/2019 8:06 AM
State (From Contact)	State	Scheduled By:	
Campaign		PA Notes	
request_id		mStaff Availability Notes	
		Referred by	

Document Retrieval

Medical Record Retrieval

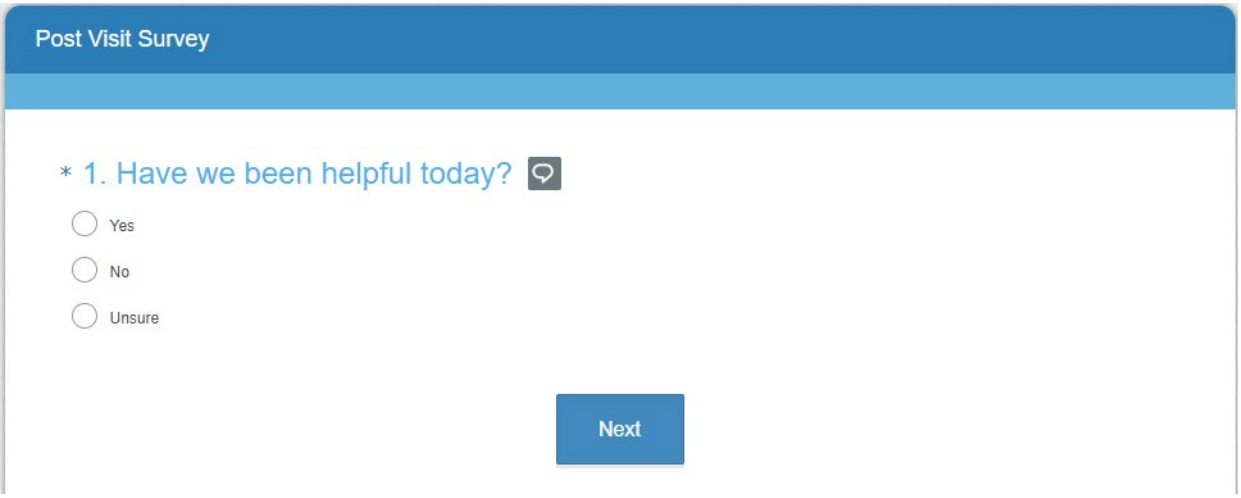
Standard Questions

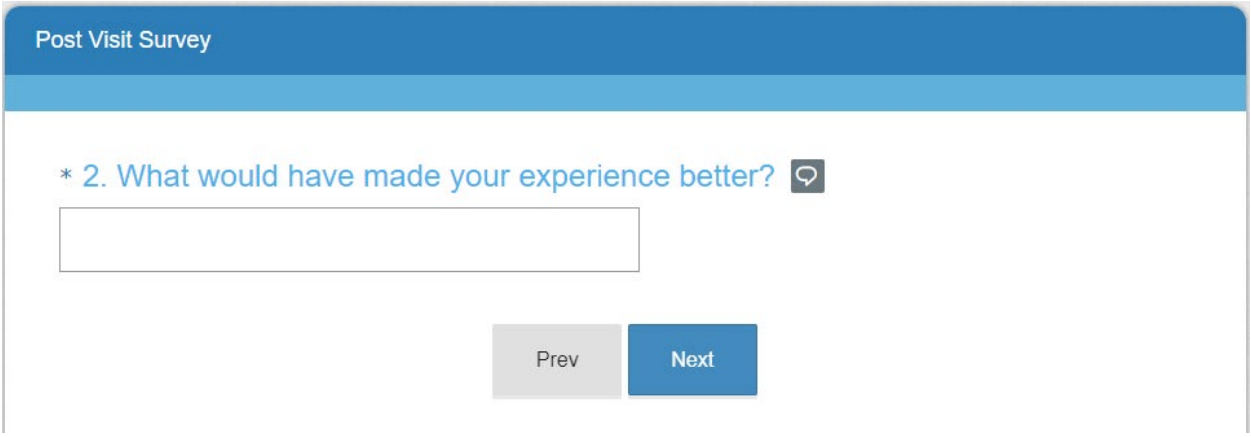
Investigational Drug in past 30 days?		Weight (in lbs)	
Currently Pregnant?	No	Height (Feet)	
Recent Blood Donation?		Inches	
		Calculated BMI	
		Total Blood Volume	

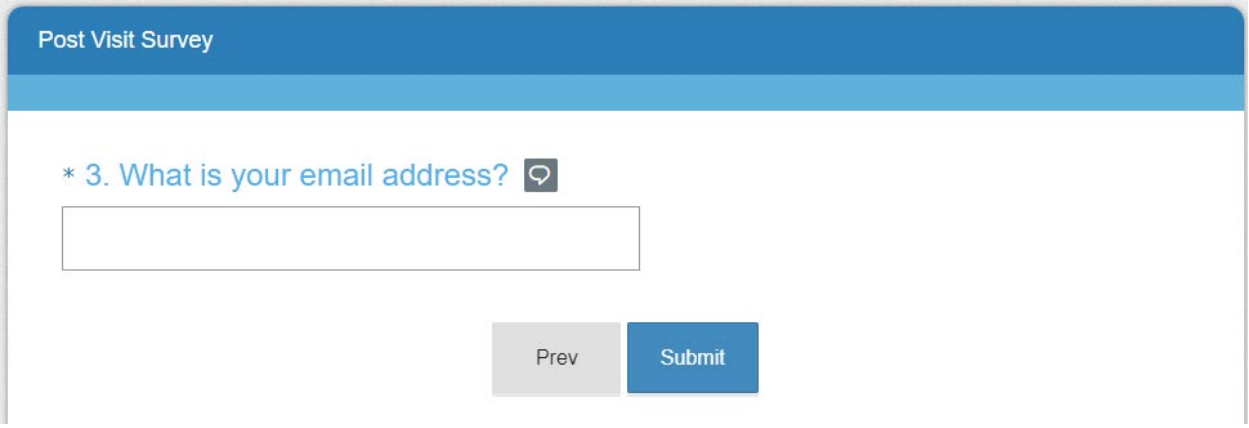
General Health

Allergies	No	Infections	No
Allergic To:		Infectious Disease:	
Autoimmune:		Cancer*	No
Auto Immune Issue:		Cancer Type:	
Gynecologic*	No	Kidney	No
Gynecologic Issues		Kidney Issue:	
Hematologic	No	Respiratory	No
Hematologic Issue:		Respiratory Issue:	
Gastrointestinal	No	Neurological	No
Gastrointestinal Issue:		Neurological Issue:	
Cardiovascular	No	Liver	No
Cardiovascular Issues		Liver Issues	
Mental Health	No	Endocrine	No
Mental Health Issuess:		Endocrine Issue:	

15 APPENDIX D –VISIT SURVEY EXAMPLES







16 APPENDIX E – ABBREVIATIONS

CFR	Code of Federal Regulations
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GINA	Genetic Information Nondiscrimination Act
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iPS cells	Induced pluripotent stem cells
IRB	Institutional Review Board
ISBER	International Society of Biological and Environmental Repositories
LAR	Legally Authorized Representative
mL	Milliliter
NIH	National Institute of Health
OHRP	Office of Human Research Protection
PBMC	Peripheral blood mononuclear cells
PHI	Protected Health Information
PI	Principal Investigator
PROs	Patient reported outcomes
RNA	Ribonucleic acid
WHO	World Health Organization