GenTAC

Policies and Procedures Manual

National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC)

Version 6

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1.0 Development of the Registry

1.1 Background

The National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) is funded by the National Heart, Lung, and Blood Institute (NHLBI) and began in September 2006. The goal of GenTAC is to develop and maintain a registry of patients with Marfan syndrome and other connective tissue diseases receiving treatments for cardiovascular complications. The registry collects data that will enable research to determine medical practices that advance the clinical management of the cardiovascular complications associated with these conditions.

Marfan Syndrome is an autosomal-dominant, inherited connective tissue disease associated with cardiovascular complications, including mitral valve prolapse, aortic aneurysmal and valvular disease, and heart failure. Premature death for Marfan patients is the result of aortic disease resulting in progressive dilatation of the ascending aorta leading to aortic valve insufficiency, heart failure, and/or aortic rupture. Cardiac surgery to treat thoracic aortic disease has improved survival. Nevertheless, Marfan patients with progressive aortic disease have a shortened life span. Treatment for Marfan-related aortic disease, including cardiac surgery, is hampered by the small numbers of patients seen, even at tertiary referral medical centers. New surgical techniques and emerging strategies need to be evaluated to improve clinical outcomes. Current surgical options include different attendant risks, but they lack independent assessment. The use of pharmacologic therapies is largely empiric and would benefit from systematic evaluation. Elucidation of the functional importance of genetic mutations associated with Marfan Syndrome has excellent potential for translation to therapeutic interventions, but is limited by difficulties in obtaining tissues for investigation and identification of kindred families by institutions with expertise in genomic applications. Animal models of Marfan syndrome demonstrate functional significance of genetic mutations and suggest new strategies for therapeutic prevention and treatment. These findings require confirmation in patients. This registry and tissue repository provides a needed resource for the evaluation of disease progression and response to therapy, data for planning appropriate clinical trials, and tissue and blood for genomic investigations, and will ultimately facilitate improved treatments for patients afflicted with genetic aortic aneurysms and other cardiac conditions.

While multiple other genetic conditions are associated with a significant risk of thoracic aortic aneurysm and dissection, far less is known about their etiology, pathogenesis and optimal medical and surgical management. Bicuspid or bicommissural aortic valve (BAV) is the most common form of congenital heart disease, occurring in about 1-2% of the population. A significant albeit undetermined percentage of individuals with this condition is at risk for ascending aortic enlargement with a predisposition for aortic tear or rupture.

Loeys-Dietz syndrome (LDS) is a dominant connective tissue disorder caused by mutations in either of the two genes that encode the TGFβ receptor (*TGFBR1* and *TGFBR2*). While this condition shows some overlap with Marfan syndrome (pectus deformity, scoliosis, arachnodactyly, aortic root aneurysm and dissection) there are other discriminating features (e.g. hypertelorism, bifid uvula, craniosynostosis, cervical spine instability, translucent skin, easy bruising, dystrophic scarring, congenital heart disease, arterial tortuosity and a high risk of aneurysms and dissections throughout the arterial tree). Most importantly, aneurysms can tear or rupture at ages and vascular dimensions that do not confer risk in other connective tissue disorders such as Marfan syndrome. Because of the aggressive and less predictable course of vascular disease in LDS, some centers advocate early and aggressive surgical intervention and the use of medications such as beta blockers or losartan to reduce hemodynamic stress or antagonize TGFβ signaling, respectively. The impact of such measures on outcome remains to be determined.

Vascular Ehlers-Danlos syndrome (vascular EDS) is a systemic connective tissue disorder caused by mutations in type III collagen. Affected individuals are at risk for life-threatening manifestations including visceral rupture and dissection or rupture of any medium-to-large sized muscular artery, with or without prior dilatation. Prophylactic surgery is strictly avoided in this population due to severe tissue friability and a high rate of life-threatening surgical complications. Precise scenario-dependent estimation of the risk-benefit relationship for surgical intervention or endovascular procedures is lacking.

Turner syndrome is a relatively common chromosomal abnormality (X0 karyotype) that can be associated with multiple vascular abnormalities including BAV, ascending aortic aneurysm and dissection and coarctation of the aorta. The proportion of people with Turner syndrome at risk for aortic aneurysm requires further definition. It is likely that evidence-based medical and surgical management guidelines for those with unequivocal aortic enlargement will derive from this registry.

NHLBI is collaborating with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Eye Institute (NEI), the National Institute of Dental and Craniofacial Research (NIDCR), and the National Human Genome Research Institute (NHGRI) in monitoring the work of the Registry to enhance the development of standard reporting of patient characteristics, indications for surgical intervention and other treatments, and adverse events. The resulting data are used to facilitate improved clinical evaluation and patient management. The Registry maintains a repository of tissue and blood, family pedigrees, and data on extra-cardiac complications. The resulting resources should also enhance future research and facilitate investigator-initiated research to improve the fundamental understanding, treatment and management of genetic aortic aneurysms and other cardiac and extra-cardiac complications.

1.2 Objectives and Scope

The broad purpose of GenTAC is to enable research to determine best medical practices for the clinical management of genetic thoracic aortic aneurysms, and other cardiovascular complications. The Registry:

- develops standard methods to collect data and specimens that are used for research to characterize patients at risk for aortic rupture and development of heart failure;
- records the demographics of patients undergoing surgical repair of aneurysms and their clinical outcomes including related costs;
- processes and creates a repository of tissue/blood specimens;
- analyzes data collected;
- provides access to these resources for Registry investigators and outside researchers interested in advancing the fundamental understanding of genetic aortic aneurysms and management of afflicted patients; and
- publishes and disseminates results.

Through the GenTAC Clinical Centers (GCCs), the Registry collaborates with hospitals and physicians in their area to collect information pertaining to patients, care providers, hospitals, and clinical interventions. The GCCs collect and ship blood and tissue specimens to the NHLBI supported tissue repository. Through its Steering Committee (SC), the Registry develops protocols to collect data and specimens to answer research questions. An NHLBI-appointed Observational Study Monitoring Board (OSMB) performs independent monitoring and analysis of clinical outcomes and adverse events. Additionally, the Registry developed a policy

for sharing data and specimens that permits Registry investigators and researchers outside the Registry to request access to these resources for research purposes.

1.3 Mission Statement

The mission of the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions is to establish a registry of patients with genetically induced thoracic aneurysms and related conditions and collect data in a bioinformatics infrastructure, as well as a repository of blood and tissue samples, that can be studied by researchers to improve the diagnosis and treatment of these patients.

2.0 NIH Organizational Overview

2.1 Sponsoring Institutes

The National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) co-sponsor this registry. NHLBI manages and has technical oversight of the GenTAC Registry contract. A NIAMS representative is included in the SC communications. The NHLBI and the investigators share responsibility for the scientific direction and performance of the registry.

2.2 Roles and Responsibilities of NHLBI Program Office Staff

2.2.1 Project Officer

The NHLBI Project Officer is involved in the scientific effort of the Registry and serves as a voting member of the Steering Committee and the Operations Committee. The Project Officer is responsible for:

- Monitoring the Contractor's technical progress, including the surveillance and assessment of performance and recommending to the Contracting Officer changes in contractual requirements;
- Interpreting the Statement of Work and any other technical performance requirements;
- Performing technical evaluation as required;
- Performing technical inspections and acceptances required by this contract; and
- Assisting in the resolution of technical problems encountered during performance.

2.2.2 Contracting Officer

The NHLBI Contracting Officer is the only person with authority to act as agent of the Government under this contract. Only the Contracting Officer has the authority to:

- Direct or negotiate any changes in the Statement of Work;
- Modify or extend the period of performance;
- Change the delivery schedule;
- Authorize reimbursement to the Contractor for any costs incurred during the performance of the contract; and
- Otherwise change any terms and conditions of the contract.

3.0 Organizational Structure

3.1 Overview

This Chapter describes the organizations participating in the GenTAC Registry, including the study chair, the eight GenTAC Clinical Centers (GCC), the Data Coordinating Center (DCC), the Biospecimen Repository, the Observational Study Monitoring Board (OSMB), and two core laboratories. It also describes the standard communication channels and addresses conflicts of interest.

3.2 Study Chair

The Study Chair directs the Registry Steering Committee and Operations Committee meetings and ensures that consensus is built and decisions are made in a timely manner. In collaboration with the DCC PI, the Chair provides scientific and administrative oversight of the Registry and contributes to decisions regarding the inclusion of database elements and the analyses of relevant outcomes. The Chair helped author these policies and procedures and ensures that the deliverables agreed to in the contract are written in such a way to reflect the goals and purposes of the Registry.

3.3 GenTAC Clinical Centers

The GenTAC Registry patients are recruited through eight GenTAC Clinical Centers (GCCs). The participating GCCs are geographically distributed academic institutions with staff that have the appropriate expertise and skills to implement a successful Registry. The GCC's provide care to patients from a wide geographic catchment area, including in the Northeast, Mid-Atlantic, South and Northwest plus the island of Hawaii. The participating GCCs include:

- Johns Hopkins University School of Medicine – primarily Mid-Atlantic and the Southeast region, as well as some nationwide and international referrals
- Oregon Health Sciences University – Oregon, Washington, Idaho, Montana and Alaska
- University of Pennsylvania Health System – Pennsylvania, Delaware, and New Jersey, as well as some nationwide and international referrals
- Weill Medical College of Cornell University – New York, New Jersey, Connecticut, and Massachusetts as well as some nationwide and international referrals
- University of Texas Medical School at Houston– Texas, New Mexico, Louisiana, Arkansas, and throughout the South.
- Baylor College of Medicine – Texas as well as some nationwide and international referrals
- The National Institute of Aging at Harbor Hospital –Mid-Atlantic region, as well as some nationwide and international referrals
- The Queen's Medical Center - Hawaii

Each GCC has agreed to cooperate in the development and design of the research protocol and abide by common methods for patient selection and enrollment, data collection procedures, tests, and reporting of results and data as recommended by the SC. In addition, each devotes comparable staff, facilities, and equipment to Registry activities. Funds are provided for a principal investigator and a research coordinator at each GCC through contractual relationships between the Data Coordinating Center (DCC) and each GCC. On average, two other investigators from each GCC participate in the study.

3.3.1 Principal Investigator

The Principal Investigator (PI) for the GCC assumes responsibility for all aspects of that Center's participation in GenTAC. The PI's responsibilities include the following:

- Serve as a voting member of the GenTAC Steering Committee and identify an alternate who may vote for the GCC when the PI is not available.
- Serve on the GenTAC Operations Committee if requested.
- Oversee the GCC budget.
- Obtain and maintain Institutional Review Board approval.
- Oversee the collection and transmission of timely and accurate data.
- Participate in and oversee local GenTAC quality assurance efforts, including site visits, response to data queries, etc.
- Hire and/or supervise other GCC personnel for the GenTAC Registry.
- Participate in conference calls, and attend network meetings as required.
- Take part in data analysis and publication activities.

3.3.2 Research Coordinator

A research coordinator at each GCC oversees the implementation of Registry activities. Under the supervision of the PI, the research coordinator is responsible for the following:

- Implementing the study protocol while adhering to policies and procedures in the protocol and manuals of operations. Activities include collection of data, image acquisition and shipment, data transmission, and data quality.
- Implementing routine quality assurance methods to be reviewed at site visits.
- Maintaining a central file of study related training and protocol materials, manuals and data forms, correspondence and performance reports.
- Collaborating as necessary with the PIs and DCC staff in the development of data collection materials.
- Assisting in efforts to obtain local institutional review board (IRB) approval.

3.3.3 Other GCC Staff

Up to two additional investigators from each GCC serve on the GenTAC Steering Committee. The expertise of these investigators should complement the expertise of the PI and should be chosen to represent the varying backgrounds relevant to the types of data being collected (e.g., genetic, surgical, medical treatment, radiology, pathology, etc.).

Additional staff may be required to abstract and transmit data or collect, process, and ship biospecimens.

3.4 Data Coordinating Center

RTI International is the Data Coordinating Center (DCC) for the GenTAC Registry. The DCC is responsible for data management, coordination of training, logistics and communications, the study website, and statistical design and analysis. In concert with the GenTAC Steering Committee and other study investigators, the DCC coordinates development of and provides input to the protocol, data collection forms, the manuals of operations, and manuscripts and presentations. The DCC assists the program staff of the NLHBI in monitoring research progress and strives to ensure data integrity, accuracy, and accessibility among all

GCCs. Finally, the DCC executes and oversees subcontracts securing the services of the GCCs. The DCC offers technical assistance and analytical support to GCC staff, as needed. Specific responsibilities of the DCC include:

- Coordinating the activities of the Steering Committee (SC), Operations Committee (OC) Observational Study Monitoring Board (OSMB), Scientific Advisory Board (SAB), two core laboratories, and other committees and work groups through provision of materials/documentation support, meeting planning and logistics, and conference call coordination.
- Helping to develop and monitor implementation of study design, data collection, and data analysis plans.
- Preparing, updating, and disseminating operations manuals, data collection forms, databases, and routine reporting summaries.
- Producing routine enrollment reports, meeting and conference call summaries, quarterly technical progress reports, semi-annual summaries, a final report and other reports as needed for the SC, OC, OSMB, SAB, and the NHLBI.
- Maintaining or assuring high quality databases resulting from all research, supervising all data collection procedures, and arranging for the most efficient transfer of study data.
- Providing interim and final limited access to study data as specified in the study protocol and manuals of operations.
- Ensuring that all sites and investigators fully comply with NIH regulatory requirements, including informed consent, reporting of adverse events, and human subject safety and welfare provisions.
- Providing training to all GCC site personnel as needed on research study implementation, data management and analysis, biospecimen collection and transport, and quality control and assurance.
- Participating in regular conference calls and attending network meetings.
- Establishing and maintaining a GenTAC Registry website with public and private portals.
- Developing procedures for biospecimen collection, processing, and transport and coordinating all activities with the Biospecimen Repository.

3.5 Biospecimen Repository

RTI serves as the designated repository for biospecimen processing and storage during the data collection phase of the Registry. The repository services provided by RTI for the registry include:

- Provision of blood collection tubes, saliva collection kits and tissue collection kits
- Provision of cryovials and freezer boxes for storage for the various biospecimen components processed locally
- Provision of appropriate shipping containers and transportation costs
- Distribution of samples to approved laboratories at the request of NHLBI

The specimens will eventually be transferred to the NHLBI repository contractor for long term storage and dissemination to future investigators. The repository will store all samples indefinitely or until the sample is used up. All samples are identified with a code number rather than subject identifying information. The repository does not have authority to distribute samples

to any investigator without a requisition generated by the DCC after approval from the NHLBI or the GenTAC Steering Committee.

3.6 Imaging Core (ICORE)

The Cardiovascular Core Laboratory at Medstar Research Institute was founded approximately twelve years ago and serves as the Imaging Core Lab (ICORE) for GenTAC. Medstar has served as the Imaging Core Lab for more than 100 multicenter clinical trials involving over 50,000 exams from more than 500 hospitals internationally. The Core Laboratory facilities occupy over 3,200 square feet of office space within the campus of the Washington Hospital Center in Washington, DC. The Core Laboratory is equipped with dedicated servers and review stations. These include: Philips Xcelera, Digisonics DigiView, Indec, and Medis workstations. Medical software and devices used in the Core Laboratory are 510K approved. The GenTAC ICORE is responsible for finalizing the image acquisition protocols and case report form as well as the receipt, tracking, reading, overreading, and storage of all de-identified images sent from the GenTAC clinical centers.

3.7 Phenotyping Core (PCORE)

Johns Hopkins University serves as the GenTAC Phenotyping Core (PCORE). Johns Hopkins University is one of the largest and most prestigious institutions in the world for the diagnosis and treatment of patients with genetically induced thoracic aortic aneurysm and connective tissue disorders. The PCORE establishes the data algorithms for validating the confidence level of the eligibility diagnoses assigned to GenTAC subjects. They work with the DCC to program the algorithms, review and interpret the results, and determine when the DCC should request additional information from the GCCs.

3.8 Scientific Advisory Board (SAB)

The Scientific Advisory Board (SAB) provides an unbiased review of proposed research and guidance on approval of Registry resources to conduct these proposed projects. The SAB is comprised of experts in the fields of medical genetics, cardiothoracic surgery, cardiology and industry specializing in the treatment of TAAD. Ad hoc members may be sought at times for review of some research proposals, if additional expertise is needed. NHLBI staff may not serve as reviewers on the committee but may participate in reviews to provide programmatic information.

3.9 Observational Study Monitoring Board (OSMB)

An NHLBI-appointed OSMB, comprised of a multidisciplinary group of experts, performs independent monitoring of overall progress, clinical outcomes, and patient safety. . The OSMB makes recommendations to NHLBI regarding appropriate protocol and operational changes. Any decision to modify the protocol or significantly change study operations may have a substantial effect upon the registry. Thus, the OSMB plays an essential role in assuring quality research.

The principal role of the Observational Study Monitoring Board (OSMB) is to regularly monitor the data from the registry, review and assess the performance of its operations, and make recommendations, as appropriate, to NHLBI with respect to:

- the performance of individual centers (including possible recommendation on actions to be taken regarding any centers that perform unsatisfactorily);
- issues related to participant safety and informed consent, including notification of and referral for abnormal findings;
- adequacy of study progress in terms of recruitment, quality control, data analysis, and publications;

- issues pertaining to participant burden;
- impact of proposed ancillary studies and substudies on participant burden and overall achievement on the main study goals;
- possible modifications to the study protocol; and
- overall scientific direction of the registry.

The OSMB is composed of a Chair and members with expertise in biostatistics, cardiology, cardiothoracic surgery, bioethics, and genetics. The OSMB meets at least annually via in-person meetings or teleconferences. Prior to these meetings, the DCC prepares and distributes reports on recruitment, progress, and data to the OSMB.

3.10 Study Communications

Good communications are vital to maintaining a collaborative network and for responding to urgent needs from policymakers. The DCC project staff work in a partnership with NHLBI, GCC personnel, and other participants to develop multiple levels of communication that foster free and open communication and encourage a spirit of common purpose and teamwork to accomplish the challenging goals of the Registry. Close communications are facilitated through several mechanisms, including e-mail, telephone and conference calls, videoconferencing, and a project web portal.

3.10.1 E-mail

Email is the primary means of day-to-day communications within the GenTAC registry. The DCC develops or forwards e-mail messages containing any information of substance to other project staff as appropriate. Email is used to communicate information to all investigators between calls and meetings.

As with all electronic forms of communication, certain precautions are necessary when using e-mail and the following precautions are taken:

- Understand that electronic mail is not private and may be subject to disclosure.
- Do not give out e-mail addresses without consent.
- Distribute messages appropriately.
- Maintain up-to-date distribution lists (e.g., GenTAC PIs, GenTAC steering committee, GCCs).
- Use the phone for sensitive information or if there is a possibility of serious disagreement or misunderstanding.

3.10.2 Telephone Conference and Other Calls

Conference and other telephone calls are scheduled as needed to foster the work of the Registry. GenTAC supports both ad hoc and scheduled conferencing calling through the use of conference meeting lines internal to the DCC when feasible.

3.10.3 GenTAC Web Portal

The GenTAC web portal serves as a source of information for both the general public and collaborators who are participating or wish to participate in the research effort. The content is closely monitored and kept up-to-date by the DCC so that the most current information is available to visitors. There are two components to the portal: a public component and a private component.

Public Website. The project website – http://gentac.rti.org – is available to the general public and is used most notably to disseminate information about the study to potential study

subjects, enrolled participants, and outside investigators interested in accessing GenTAC data for ancillary studies. The public pages includes:

- project description and rationale,
- participating institutions and contact information,
- links to project newsletters,
- study protocol,
- instructions for requesting access to data and biospecimens,
- list of publications and copies of abstracts,
- links to organizations which provide information and resources about the conditions under study (e.g., NMF), and
- an entry point to the private website.

Private (Restricted) Website. Services provided in the private component are intended for GenTAC Registry researchers and staff and are only accessible to registered users. The private area of the study website provides a secure, unified communication channel for all GenTAC activities and provides access to the data capture and data management systems, as well as maintain the repository of registry materials, documentation, and reports. The private component also provides links to investigator proposals, Steering Committee meeting and conference call minutes and materials, and minutes from other registry conference calls, and consultation meetings. Registered users may click on the links to view or download meeting agendas, rosters, PowerPoint presentations, materials distributed at meetings, and other study related documentation. Links to Registry publications are included within copyright regulations. This ensures that all research staff have one place to access all GenTAC information and study systems. Access to information and systems through the portal is authenticated for users based on the definition of study roles. These roles allow access only to those systems needed by a particular user to carry out the responsibilities of his/her role. Role-based access protects data confidentiality and security and increases data integrity.

At this time, there are two levels of access to the private section: GenTAC network participants and GenTAC researchers. GenTAC researchers are those individuals invited to participate in GenTAC meetings. The GenTAC researcher level of access grants users access to documents related to the meetings which they attended. The GenTAC registry network level of access grants users unlimited access to the entire private component of the portal.

Registered user accounts are created and maintained by the DCC. Each research group has a designated portal contact person who is responsible for updating the list of portal users sponsored by that research group. Requests for new user accounts must be made to the portal administrator by each research group's portal contact. Each portal contact notifies the portal administrator of any changes to the user list including both user accounts that should be created and those that are deleted as staff discontinue participation in Registry activities. Registered users are given user IDs and passwords to access the private component of the website.

3.10.4 GenTAC Logo

A GenTAC logo was developed to help increase public and scientific awareness of the breadth and depth of activities associated with the Registry. The GenTAC logo should be used on all GenTAC–related and GenTAC–supported materials when feasible. The logo is available through the DCC.

3.11 Conflicts of Interest

A conflict of interest policy has been drafted to promote objectivity in research by establishing standards to ensure there is no reasonable expectation that the design, conduct, or reporting of research funded under this study is biased by any conflicting interest of an Investigator and/or study personnel (collectively referred to as “investigators”).

This policy sets forth the principles for identifying the potential for conflicts and the procedures for reviewing and minimizing, managing, or eliminating any conflicts that might occur. This policy shall be adhered to in addition to any obligations that are required by Federal, State and/or your Institutional policies.

Each participating investigator is expected to file an NHLBI Financial and Conflict of Interest Disclosure form and must update the form if a real or apparent conflict should arise. The original form shall be filed with the Data Coordinating Center and a copy maintained in the site regulatory binder. Participating investigators entering the registry shall file the disclosure form prior to becoming involved in the registry.

3.11.1 Conflict Of Interest and Financial Disclosures Policy

The Registry and the National Institutes of Health are committed to ensuring that any real or perceived conflict of interest with its investigators are to be avoided. Specifically, any real or perceived conflicts that would bias the study design, conduct, and data analysis and interpretation of the clinical research must be avoided. Conflicts of interest, in the most conventional sense, arise because investigators may have the opportunity to influence the study’s decisions in ways productive to personal gain. Because of the potential that a real or apparent conflict of interest could bias conclusions, and because even the perception of a conflict of interest could compromise research credibility, participating individuals should make reasonable efforts to avoid the occurrence of such conflicts.

It is the policy of the Registry that:

- All investigators have an obligation to avoid ethical, legal, financial, or other conflicts of interest that reasonable peers or an informed public could construe to conflict with the investigator’s unbiased contributions to the registry or its welfare;
- Any investigator engaging in an outside activity or possessing a personal interest that could lead to a conflict of interest must inform the Registry Principal Investigator of that possibility; and
- Relationships between investigators and outside institutions must not impede the unbiased conduct of the registry or open communication of research results.

3.11.2 Implementation of the Policy

The Registry is committed to the implementation of its Registry Conflict of Interest and Financial Disclosures Policy by providing for:

- Disclosure of all relationships (financial and otherwise) that may result in conflicts by persons subject to the policy;
- Readily available counsel and advice regarding all conflicts real, possible or potential; and
- Fair and equitable application of the policy to all investigators.

The requested disclosure attempts to balance the Registry’s need for information with the participants’ reasonable expectation of privacy in their personal affairs. The following guidelines will assist investigators with disclosure.

3.11.3 Principles Defining Conflicts Of Interest among Registry Investigators

- Test Product. A test product includes a drug, technique, or technology and the ancillary materials tested and/or evaluated in the aegis of the registry, such as training materials, in support of the drug, device, technique or technology.
- Immediate Family Member. Immediate Family Member includes a spouse and dependent children.
- Conflict of Interest. There are several types of situations that could constitute a real or apparent conflict of interest:

    1. Professional Interest

        a. The participating individual or an immediate family member has played a substantial role in the prior development of a product or technology that is being utilized by and currently receives financial or other material benefit from such product or technology. Disclosure is not required in the absence of a current financial or other material benefit.

        b. The participating individual or an immediate family member has a substantial ongoing affiliation with an organization having a role in the development or sale of a product or technology that was developed by or is being utilized by the registry, including organizations holding patents to or licenses for the development or sale of research products. That would include instances in which the individual serves as an officer, director, trustee, general partner, or employee for such an organization regardless of whether the participating individual is currently being compensated for that position. Such organizations would also include those with which the individual is negotiating for or has an arrangement concerning prospective employment or affiliation, or those from which the participating individual receives or expects to receive compensation in the amount of $10,000 or more annually for laboratory activities, honoraria, consultative services, or other activities (such as educational grants). The significance of the conflict will depend, to some degree, on whether reimbursement for professional activities involves compensation limited to that normally required to support the scientific process, or is substantially larger, leading to actual or potential personal financial gain to the investigator or an immediate family member.

    2. Proprietary Interest

        a. The participating individual has a financial interest in the research product being studied because the individual or an immediate family member has a material interest in the product or technology that may result in financial gain, e.g., where the individual may receive royalties or other compensation following the commercial sale of the product or technology. Such royalties may be in the form of personal compensation to the individual or may be used in support of the individual's research.

        b. The participating individual has a financial interest in the research product being studied because the individual or an immediate family member has an equity interest or option of $10,000 or more in a commercial enterprise that will benefit from the sale of the product or technology.

        c. Disclosure of financial interests is also required when an extended family member (independent children, siblings, parents) holds an executive position in

the business, or holds equity or ownership interest valued at ten (10) percent or more in a business.

- There may be other instances in which a participating individual or an immediate family member has an affiliation or relationship such that objective impartiality could be questioned. The standard that a participating individual should use in determining whether or not to disclose a real or apparent conflict of interest is how the conduct in question would look if reported in the *New York Times*.
- The conduct of core laboratory studies represents another area of potential conflict of interest for Registry investigators. Investigators must disclose consulting relationships, executive positions, or significant financial interests in a business that markets, produces or conducts pre-market testing of a commercial device or product that will be used in the acquisition or processing of all core laboratory studies.

The intent of this operating policy is to err on the side of full disclosure. Thus the participating individuals may need to disclose any other interests, affiliation, arrangements or relationships that could lead to questions about the motives in connection with their work on behalf of the registry if such interest, etc. were known or made public. In any such instance, the participating individual should disclose the nature and extent of such affiliation or relationship.

Failure to disclose a financial interest or a conflict of interest as required could result in the loss of privilege to participate in the activities of the registry.

3.11.4 Review Process for Evaluation of Disclosed Relationships For Actual Conflicts of Interest

All registry investigators are required to fill out and submit the Financial and Conflict of Interest Disclosure Form before beginning work (i.e. patient screening, etc.) under this study and on an annual basis thereafter. The disclosing party has an obligation to update the Disclosure Form more frequently than annually if information changes that may suggest development of a potential conflict of interest.

The Coordinating Center is responsible for review of the disclosure documents, which are kept confidential and secure, and is responsible for ensuring that discussions and decisions made by the leadership group are not influenced by those with identified conflicts of interest. The DCC Principal Investigator and GenTAC Study Chair have ultimate responsibility to ensure that the process for decision making, analysis and interpretation and reporting of study results in the Registry, is objective and unbiased without any real or perceived conflict of interest.

Committee and subcommittee chairs also are responsible for reminding members of their groups of the need for declaring conflicts of interest when deemed appropriate (i.e. discussion or voting on recommendations that might be perceived as conflicts of interest in light of personal financial disclosure).

The Principal Investigator's disclosure documents are reviewed by the Study Chairman. The Study Chairman's disclosure documents are reviewed by the NHLBI Project Officer.

4.0 Committees, Subcommittees, and Working Groups

A number of committees, subcommittees, and working groups have been formed across the life of the registry. The Steering Committee (SC) and an Operations Committee (OC) provide the overall guidance and daily management of the GenTAC contract. A Publications Committee oversees the publications process. The Ancillary Studies Committee reviews and recommends approval of ancillary studies. Additional subcommittees and working groups are formed as needed to address specific aspects of the study.

4.1 Steering Committee

The Steering Committee (SC) is GenTAC's main governing body and serves as the focal point for communication, exchange of ideas, development and management of joint protocols and research activities, and problem resolution. The SC establishes the scientific direction of the registry and has primary responsibility for the selection of Registry topics for research (within constraints of the budget), overseeing the development and conduct of the registry protocol (including implementation and monitoring), and the preparation of publications.

Members of the SC communicates through regular conference calls, e-mail and at least annual in-person meetings. Written minutes of meetings and conference calls are available within 15 days and posted on the project website.

4.1.1 Membership

The Steering Committee membership consists of the Study Chair, the NHLBI Project Officer, the Principal Investigator (PI) of the DCC, the Principal Investigator from each of the eight GCCs, and the Principal Investigator from each of the two Cores.

4.1.2 Voting Procedures

The Study Chair, the NLHBI Project Officer, the PI of the DCC, and the PI from each of the GCCs and the two Cores are voting members of the Steering Committee. If a PI from a GCC or the DCC is absent from a particular meeting or conference call, the PI may designate a co-investigator to serve as the voting member for the institution for that meeting or call by notifying the DCC in advance. Each of these eight individuals has one vote on motions before the committee.

A quorum is considered present if five voting members are present or vote on an issue in person of through e-mail or over the phone.

The voting members decide issues that have a scientific impact on the direction of the Registry. Unless otherwise specified, all scientific decisions shall be based on a simple majority of those present and voting as long as a quorum has been achieved.

Each motion and vote is recorded in the minutes and assigned a number for tracking. Each motion is maintained in a chronological log by the DCC for easy retrieval.

The vote of the Study Chair breaks a tie, if necessary. The Study Chair reserves the right to delay a critical vote if necessary to achieve a consensus.

4.1.3 Meetings and Attendance

The Steering Committee meets monthly by teleconference and holds at least one annual in-person meeting. In general, meetings include discussions of data collection and research progress. The input of each member is fundamental to the operation and advancement of the Registry. Should a PI find it impossible to attend a Steering Committee meeting, s/he is required to notify the DCC Principal Investigator of the expected absence, and ensure attendance of an alternate voting member.

4.2 Operations Committee

The Operations Committee (OC) is a subcommittee of the Steering Committee with oversight and authority for the daily operations of the study.

4.2.1 Membership

The Operations Committee consists of the Principal Investigator and Senior Project Manager of the DCC, the Study Chair, and the NHLBI Project Officers and Clinical Trials Specialist.

4.2.2 Meetings

The OC holds weekly meetings by teleconference to discuss study progress.

4.3 Publications Committee

The Publications Committee develops written publication policies that address data and tissue access (Registry-wide, site-limited, and external researcher), data analysis, preparation of manuscripts and other scientific reports, and authorship. In addition, the committee develops a process for review of all manuscripts and abstracts prior to submission to the Steering Committee for clearance. The goal of this subcommittee is to ensure timely submission of high quality manuscripts and appropriate authorship credit. The publications policy for the GenTAC Registry is described in **Chapter 10** of this document.

4.3.1 Membership

The members of the Publications Committee include the PIs from each of the participating organizations and the Study Chair.

4.3.2 Voting

A quorum consists of five voting members of the committee. Each member has one vote, and a simple majority is required to reach a decision. In case of a tie, the Steering Committee Chair casts the deciding vote.

4.3.3 Meetings and Operations

Meetings are called as necessary to address issues related to publications and are held in conjunction with Steering Committee calls and when feasible.

The DCC coordinates the activities of this committee and maintains a listing of the publications and presentations associated with the Registry.

4.4 Ancillary Studies Committee

The GenTAC Steering Committee developed a policy for the submission, review and approval of ancillary studies and an Ancillary Studies Committee will be appointed to oversee the implementation of this policy. An ancillary study is one that derives support from funds other than the GenTAC contract. Examples include studies funded by investigator-initiated NIH research awards (R01s), grants from academic institutions, private sources (e.g., drug companies), or those performed at no cost (generally because of the special interest of a researcher). GenTAC investigators are encouraged to consider ancillary studies and to involve other investigators within their institutions in this process. Ancillary study proposals will also be considered from non-GenTAC investigators and institutions.

The Ancillary Studies Committee reviews all proposals for ancillary studies and makes recommendations to the Steering Committee regarding approval of each proposed study. The first level of review for a proposed ancillary study is to determine whether it will interfere with other parts of the GenTAC protocol and whether the proposed study will hamper continued participation in the registry or provide undue burden on patients or the DCC. The scientific merit of a proposal is also reviewed. The complete ancillary studies policy is described in **Chapter 9** of this document.

4.4.1 Membership

The members of the Ancillary Studies Committee are the SC Chair, the eight GCC PIs, the NHLBI Project Officer, and the DCC PI.

4.4.2 Voting

A quorum consists of five voting members of the committee. Each member has one vote, and a simple majority is required to reach a decision. In case of a tie, the Steering Committee Chair casts the deciding vote.

4.4.3 Meetings and Operations

Meetings are called as necessary to address issues related to ancillary studies.

A DCC staff member is assigned to help coordinate the activities of this committee and to maintain a listing of the ancillary studies associated with the Registry.

4.5 Imaging Subcommittee

The Imaging Subcommittee develops procedures for transfer of imaging studies to the ICORE and identified the data to be read from each image.

4.5.1 Membership

The members of the Imaging Subcommittee are the ICORE Investigator and representatives from each of the eight GCCs.

4.5.2 Meetings and Operations

Meetings are called as necessary to address issues related to ICORE operations. A DCC staff member is assigned to help coordinate the activities of the committee.

4.6 Phenotyping Subcommittee

The Phenotyping Subcommittee establishes the data items needed to create algorithms and verify diagnostic categories.

4.6.1 Membership

The members of the Phenotyping Subcommittee are the PCORE Investigator, DCC statistician and another DCC representative.

4.6.2 Meetings and Operations

Meetings are called as necessary to address issues related to PCORE operations.

4.7 Media and Promotions Subcommittee

The Media and Promotions Subcommittee works with the NHLBI, SAB and other committees to promote the use of registry resources and investigate the options for transitioning the Registry to another funding source at the conclusion of NHLBI's support in September 2016.

4.7.1 Membership

The members of the Media and Promotions Subcommittee are the DCC PI, the Study Chair and senior project manager. Additional ad hoc members may be included depending on the promotion activity.

4.7.2 Meetings and Operations

Meetings are held as necessary to address issues related to promotion.

4.8 Genetics Subcommittee

The Genetics Subcommittee oversees the collection of genetic information and its integration into the overall GenTAC registry database. Genetic information refers to raw genetic data obtained from GenTAC biorepository material, review of subject medical records and appropriate data from GenTAC forms, which includes (but is not limited to):

DNA sequencing
Genotyping - SNP analysis from GWAS studies or targeted genotyping

Copy number variation
Epigenetic data (DNA methylation status)
Chromosome analyses (karyotype, FISH)
Microarray

4.8.1 Membership

The members of the Genetics Subcommittee are investigators from the GCCs with a special interest in genetics, the DCC PI, a genetic epidemiologist from the DCC, and the NHLBI Project Officer (or other GenTAC team member from NHLBI). Additional ad hoc members may be included depending on need.

4.8.2 Meetings and Operations

Meetings are held as necessary to address issues related to the transfer and sharing of genetic data.

4.9 Working Groups

Working groups are developed as necessary to address specific areas of interest or to facilitate operations of the GenTAC Registry. At least one representative from NHLBI, one staff member from the DCC, and one GCC PI participate on each working group in order to provide a liaison between the Steering Committee and the Working Group. Although a number of working groups may be formed, the following sections address working groups likely to be integral to study operations.

4.9.1 Research Coordinators Working Group

Research Coordinator Working Group calls are held on a monthly basis for the purposes of training, review of protocols, addressing common issues related to study conduct, the preparation or initiation of ancillary studies, and introduction to new or revised study software or other procedures. The trained and certified research coordinators are be responsible for certification of staff in their center, including nurses, chart abstractors, data entry personnel, and pharmacists, using procedures developed by the SC, the DCC, and the NHLBI Project Officer. Research coordinators participate, by invitation, in site visits and Steering Committee meetings on an ad hoc basis.

4.9.2 Writing Groups

Writing Groups are formed for each publication. The writing group submits a concept sheet for review by the Publications Committee prior to beginning a manuscript. Through this process, other interested investigators have the opportunity to indicate and interest in joining the writing group. This group is responsible for drafting the manuscript, for soliciting input from other investigators as required, and for submitting the manuscript to the Publications Committee for review as required by the Publications Committee. Rules for authorship are described in **Chapter 10** of this document.

5.0 Human Subjects

5.1 Introduction

No data collection activities occur at an individual data collection site until approvals from NHLBI, RTI, and the GCC-specific IRBs have been granted. At the start of the study, the GCCs and RTI concurrently submitted the protocol, consents, and data collection forms to their respective IRBs for review. Upon approval, the signed documentation was sent to the DCC and to NHLBI with a request to begin patient enrollment. No contacts with potential study subjects at a study site takes place prior to NHLBI approval to commence enrollment at that location. All participating institutions and RTI are required to have a Federal Wide Assurance (FWA) issued through the US Office of Human Research Protections which assures that the organizations are

complying with all Federal regulations to protect research subjects. If GCCs collect data through outlying hospitals or practices, each hospital or practice is required to have both an FWA and IRB approval in effect.

5.2 Federal-Wide Assurance

Per federal regulations, an institution that is "engaged" in federally-supported research that involves human subjects, must file an "Assurance" of protection for those human subjects. Assurances are intended to protect human subjects who are involved in research federally-funded by the U.S. government. In this case, NHLBI and other NIH Institutes and Centers support the research. Federal-Wide Assurance (FWA) is an assurance of protection for human subjects (as prescribed in 45 CFR, Part 46), filed with the Health and Human Service Office (HHS) for the Office of Human Research Protections (OHRP). Assurances obtained by means of the FWA cover all federally funded human research. It is imperative to note that each legally separate institution needs its own FWA prior to receiving an award from NHLBI and before participating in data collection activities. These assurances are valid for three years and must be renewed so that the Assurance is valid throughout the study. The following web site contains more information on FWA and human subject involvement regulations: http://www.hhs.gov/ohrp/.

5.3 Institutional Review Boards (IRBs) and IRB Approvals

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are being taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents, data collection instruments, and investigator brochures) to ensure protection of the rights and welfare of human subjects of research. IRB clearance must be obtained for each phase of the study before participants are approached, including pilot studies, the main protocol, and each ancillary study implemented at a site. IRB approval must be obtained again each time there is a change to a protocol that affects the rights of the human subjects participating in the activity, and each time any change is made to the Consent Form for the activity. IRB approval also must be updated at least annually for each activity (or for the study as a whole).

The OHRP website above contains documents designed to guide the development of appropriate and comprehensive consent forms. It is the responsibility of the Institutional Review Board to ensure that the informed consent document complies with the regulations governing informed consent. All clinical research projects must comply with the universally-accepted principles of Good Clinical Practice (GCP) as outlined in the Federal Code of Regulations 21 part 312 or the International Congress on Harmonization's Guidelines to Good Clinical Practice. The DCC developed model consent forms meeting regulatory requirements for the Registry. The DCC can assist in the development of materials related to obtaining and documenting informed consent for ancillary studies if requested.

Additionally, IRBs monitor patient safety. Thus they should be notified of unexpected adverse events. They should be immediately notified when serious adverse events occur. Since the Registry is collecting mostly observational data, adverse events are not expected as a result of the study. However, adverse events could occur as a result of biospecimen collection or social or psychological harms could occur through the unintentional identification of Registry participants. Any adverse events that could be associated with participation in the Registry are reported to the IRBs and to the OSMB. Reporting of adverse events will be discussed in protocols for Ancillary studies as expected events for those studies are unknown at this time.

According to federal regulations, each GCC must submit relevant information for protocols in which it is participating to a local IRB for review and approval of the procedures developed to protect the rights of human subjects participating in the activity. Enrollment in the

Registry or any ancillary GenTAC study cannot begin data collection until the DCC has received documentation of current IRB approval.

5.3.1 Record Keeping

Each GCC must obtain appropriate documentation supporting its IRB reviews and the protection of human subjects at all participating institutions and have them readily available for inspection at either location. The specific documents that must be kept on file include:

- Listing and contact information for IRB members at each institution;
- IRB meeting minutes that cover the review of the study protocols and consent forms for all studies and activities in which it is participating (IRB approval must be obtained before approaching any potential participants, must be updated each time there is a change to the protocol or consent forms and at least annually until the activity concludes, and copies of the approval documents and approved consent forms must be sent to the DCC);
- GCC's responses to IRB comments;
- IRB approval document along with copies of the Protocol and Consent form approved by the IRB at that time; and
- Other IRB meeting minutes discussing the study protocol.

These documents should be clearly labeled and easily accessible at the project site.

To help ensure the safety of subjects enrolled in NIH-funded studies, the following information must be sent to the DCC in a timely manner as specified in this section. The DCC notifies NHLBI of the receipt, evaluation of, and response to this time-sensitive information.

The DCC must be informed of all major changes in the status of ongoing protocols:

- all amendments to a protocol,
- termination of a protocol,
- temporary suspension of the protocol,
- any change in informed consent or IRB approval status, and
- temporary suspension or permanent termination of patient accrual.

Notification of any of the above changes of status must be made within 7 (seven) working days of the change of status notification to or from the local IRB.

5.4 Human Subjects Training and Documentation

NIH requires education on the protection of human research participants for all individuals contacting patients or having access to patient data for contracts involving human subjects. Prior to beginning data collection, each GCC must send a description of education completed in the protection of human subjects for each participating individual to the DCC. If staff are replaced or additional staff begin work on GenTAC, documentation of their human subjects training must be sent to the DCC. Each clinical site PI and the DCC PI are responsible for ensuring that their personnel have completed an approved training program.

Many institutions have developed programs that meet these requirements. Although NIH and the DCC do not endorse particular programs, curricula are available that can provide guidance or that can be modified to provide training in this area. See http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp for computer-based training developed for NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics. All training

programs developed by the DCC include a component on the protection of human subjects and informed consent as it pertains to GenTAC, but this component is not detailed enough to meet the general education requirement.

5.5 HIPAA

The Health Insurance Portability and Accountability Act (HIPAA) requires that all research collecting identifiable health information on an individual be in compliance with HIPAA standards and regulations. HIPAA regulations specifically apply to research studies collecting Protected Health Information (PHI).

PHI is defined by HIPPA as health information transmitted or maintained in any form or medium that:

- Identifies or could be used to identify an individual, and
- Is created or received by a healthcare provider, health plan or employer, and
- Relates to past, present or future physical or mental health or condition of an individual.

Given that GenTAC utilizes participants' PHI, all clinical sites comply with the HIPAA regulations as they relate to research.

Compliance for each clinical site requires that each subject read and sign a hospital specific form "HIPAA Authorization to Use and Disclose Individual Health Information for Research Purposes". This may be combined with the consent form or may be separate. Registry participants receive a copy of the signed authorization. Importantly, the "Certificate of Confidentiality" issued for the protocol helps assure protection of the PHI data (see Section I.3.4).

5.6 Confidentiality Procedures

5.6.1 Retention, Protection, and Use of Identifying Information

Full names and other identifying information, excluding date of birth, are retained only by the GCCs. Participants' data and biologic samples are labeled with coded identification numbers that can be linked to names only by the corresponding GCC. GCCs may contact patients every 6 months to collect current contact information, which assists in retention for follow-up. Personal identifying information, such as full name, address and social security number are not provided to RTI or NHLBI. RTI will maintain a separate file of subject's first name and State of residence in order to identify possible duplicate or overlapping pedigrees and family members that are enrolled in the registry.

5.6.2 Confidentiality of Data

All collected data is kept confidential to the extent permitted by law. The study coordinator at each GCC is trained in the requirement for maintaining confidentiality. In addition, a Certificate of Confidentiality to limit the possibility of forced disclosure under subpoena or other legal action has been obtained through the NHLBI. The DCC is not able to link an individual to their identifying information.

Data Coordinating Center (RTI). Hard copy files are be stored in a locked filing cabinet with access only to authorized study personnel. A comprehensive set of IT security measures is applied to all data collection and processing systems. These controls are appropriate for the Level 2 security described in the DHHS Matrix of Minimum Security Safeguards (i.e., NIST Moderate). These measures include a combination of physical security controls, operational controls, technical controls and management controls. All security controls are discussed in detail in the project specific IT security.

Briefly, there is a project website with a secure, gated application. Access is restricted and only authorized users are allowed entry into specific areas and are granted certain functional privileges. Access is controlled via security roles which are administered by RTI. Only members of certain security roles have view and/or edit permissions within the website.

Transmission of data keyed through the access restricted area is secure using Secure Socket Layer (SSL) technology. SSL is a security protocol that has become the universal standard for authenticating Web sites to Web users, and for encrypting communications between users and Web servers. SSL allows users to send and receive information in an encrypted manner as it travels through the many computers and networks before reaching its final destination. Because SSL is built into all major browsers and Web servers, simply installing a digital certificate, or Server ID, enables SSL capabilities

Additional standard data security procedures include daily incremental and weekly full backups of keyed data. These general procedures allow for daily copying of changed data sets to tape and weekly backups of the entire data archive. All backup tapes are stored in an offsite location.

GCCs. Copies of medical records may be kept at the clinical sites for research purposes. All copies of medical records and the linkage between a participant name and study ID will be maintained indefinitely in the event that patients need to be recontacted. Biospecimens and information from the interview and medical records collected for the study are de-identified and marked with the subject ID number only. Any results of this study reported in medical journals or at meetings do not identify individuals.

Biological Specimens. Any blood components or tissue samples collected for study purposes are marked with a specimen ID number only. The local PI and the DCC maintain a record that can link these collected specimens with the individual they came from; this record is maintained in a secure location (e.g. locked file cabinet or electronic file with adequate protections established) and will be destroyed within seven years of study completion.

5.6.3 Certificate of Confidentiality

A Certificate of Confidentiality (COC) has been obtained for GenTAC from the National Heart, Lung, and Blood Institute (NHLBI). This COC prevents study personnel from being forced to disclose information obtained from interviews, chart abstraction or biological sample analyses.

5.6.4 Protection of Subjects

Participant safety always takes priority above all else. Toward this end, GenTAC adheres to the International Conference on Harmonization's general principles of Good Clinical Practice. These principles dictate, first and foremost, that we have weighed and continue to weigh the anticipated benefits versus the foreseeable risks to all participants. Participants are fully informed of these risks before they are enrolled. Close monitoring of participants' adverse events occurs throughout the study. The GenTAC Steering Committee will continually review the literature to determine if new findings substantially affect the Registry's rationale or justification, or if new or previously unforeseen risks must be conveyed to participants. The study's leadership will share any such findings with the OSMB and the NHLBI Project Officers in a timely manner so informed decisions can be made about continuing the study.

Assurances of participant safety are made through informed consent procedures, responsibilities for participant confidentiality, adherence to HIPAA regulations, and close monitoring and reporting of adverse events.

5.7 Unbiased Recruitment

All eligible participants are recruited without bias. Genetically induced thoracic aortic aneurysms and related cardiovascular conditions under study are known to occur in all genders, races, and age groups. Children, women and minorities are included as much as possible in the GenTAC registry. Each GCC provided a breakdown of targeted patients by age and gender (see protocol). Breakdowns by race and Hispanic origin were not available, but are monitored closely during the enrollment phase.

5.7.1 Inclusion of Children

Children are included in the GenTAC Registry to the extent that they exist in the population being studied and meet eligibility criteria set forth for study participation. Marfan, Loeys-Dietz, and Turner syndromes are usually diagnosed in childhood. In addition to parental/guardian consent, child assent is obtained from children at least 8 years of age, or as determined by the local IRB, up to age 17. All patients under the age of 8 are consented solely by their parent or guardian.

5.7.2 Inclusion of Women and Minorities

We recognize the importance of having all eligible persons participate in this study, and we are particularly conscious of the need to include women and minorities in the study population. The DCC monitors each GCC to assure recruitment of women and minorities who meet eligibility criteria. This study's selection criteria include all individuals who fit the inclusion criteria, without regard to sex, race, or ethnic group. Aortic aneurysms are not known to have a significant sex or race bias in terms of disease prevalence, and the expected enrollment figures for each GCC reflect the demographics of the site population as a whole.

5.7.3 Target Enrollment

During the first phase of GenTAC, 2296 subjects were enrolled across five GCCs. Under Phase II of GenTAC, the new recruitment targets are reduced and vary by each of the eight GCCs. The table below presents the target overall enrollment goals for GenTAC.

Target enrollment for Phase II of GenTAC

	Original sites						New sites		
	COR	JHU	PEN	OHS	UT	BAY	NIA	QMC	TOTAL
No. enrolled GenTAC phase I	547	474	502	395	210	168	--	--	2296
GenTAC phase II Target	275	200	275	175	200	100	150	150	1525
TOTAL ENROLLMENT	822	674	777	570	410	268	150	150	3821

The enrollment targets were reduced from the first phase of GenTAC for a number of reasons, including:

- Concentration on conducting follow-up during Phase II of GenTAC,
- A focus on new patients that have complete phenotyping, have an image available for the ICORE, and are available for follow-up, and
- An increase in other responsibilities at the GCCs.

The eight participating GCCs treat patients from different parts of the U.S., and from a mix of urban, suburban and rural environments. Hence, the Registry should be adequate to provide basic descriptive information on variation in health outcomes according to patient demographic and health characteristics with some information on impact of population density and regional differences. As important, since referral for diagnosis is likely to occur at the primary care physician level, the Registry may be able to detect regional variation in patterns of diagnosis, adequacy of monitoring, and frequency of preemptive versus emergency surgical procedures. The addition of two new sites, QMC and NIA into GenTAC Phase II, enhances the Asian/Pacific Islander and the Ehlers-Danlos patient populations, respectively.

5.8 Informed Consent

5.8.1 Overview

Written informed consent is obtained from all participants or their legal guardians. Consent is obtained by study-related personnel who are knowledgeable of the study and who have knowledge and training in the consent process and in protection of human subjects. No study-related procedures (sample collection, chart abstraction) is undertaken before a signed consent form has been completed by the subject or his or her guardian. In addition to parental/guardian consent, child assent is obtained from children at least 8 years of age, or as determined by the local IRB, up to age 17. All patients under the age of 8 are consented solely by their parent or guardian.

5.8.2 Consent and Assent Procedures

During the process of obtaining informed consent, potential participants have the nature of the study, specimen collection, data collection procedures, the importance of compliance to study procedures, and the potential risks and benefits explained to them. Potential participants are told that there is no obligation to participate, that there is no penalty for declining to participate, and that their treatment will not be compromised if they choose not to participate or cease participation at any time.

Ample time is provided for each potential participant to read and understand the consent form and to ask questions. If a potential participant and/or legal guardian (if applicable) cannot read, the consent form is read aloud or an audio-tape of the consent form and a tape player will be provided. Written consent forms and formal interpreters are available to conduct informed consent in English and Spanish. When possible, written translations and formal interpreters for conducting informed consent in other languages.

An individual who consents to the study is given a copy of the signed consent form for personal records. Guardians are given a copy of the signed assent form for minors. A copy of all signed forms is placed in the medical record (if required). The original signed forms is kept in a locked file at the clinical site with other confidential information on the participants.

5.8.3 Family Members as Secondary Research Subjects

The Registry is cognizant of the concerns and limitations placed on obtaining identifiable health and private information about relatives from study subjects (Botkin, 2001; Resnik and Sharp, 2006). Waivers to informed consent will be requested from the IRB committees at the GCCs, other participating clinical sites, and the DCC. Waivers should be granted if 1) the research involves no more than minimal risk, 2) the waiver will not adversely affect the rights and welfare of the family members, 3) the research could not practicably be done without the waiver, and 4) when appropriate, the family members will be provided with additional pertinent information after participation. Strong data security systems will be in place to prevent any breach of privacy or confidentiality.

5.8.4 Parents of Minors as Primary Research Subjects

If the consenting parent of minor subjects are completing the Family History Form, the parent signs a consent form in order to provide information about their personal health. The consent form signed by the guardian for the child participant serves as a combination parental permission and parent consent form.

5.8.5 Risks and Benefits

The data collected for this Registry are from medical record abstraction, patient interviews, blood collection and remnant tissue. The interviews are not considered greater than minimal risk but may trigger uncomfortable feelings about one’s lifestyle, quality of life or personal or family history of disease. There are no direct benefits to the participants in this registry. Some patients may benefit from knowing that they are helping to advance knowledge for future patients with their condition.

5.8.6 Rights of Refusal and Withdrawal

Patients are free to refuse enrollment or withdraw from the study at any time. Participants may refuse to answer individual questions on the self-administered questionnaire or may refuse the questionnaire entirely. In the case of withdrawal, participants have the right to request that their biological specimens be destroyed.

5.9 Access to Registry Data Results by Participants

Findings from this study may or may not have clinical implications to research participants. There is no plan to return individual test results to patients or their physicians. However, if testing on study samples determines a study subject or their family is at risk for a disease or complication, the GCC PI is informed and encouraged to discuss the results with the patient. Every enrolled patient has the right to request test results determined on their study samples by submitting a written request to the PI at their GCC. Testing that is done by an outside investigator as part of an approved ancillary study is not considered part of the patient's study record and is not sent to the DCC or made available to study subjects.

6.0 Quality Assurance

6.1 Overview

Quality assurance is maintained by the following processes, procedures and steps:

- Development of a standard protocol, data collection instruments and manual of operations;
- Development and implementation of an appropriate data management system that has undergone code review, unit testing and integration testing;
- Training and certification of GCC staff;
- Data entry screens that replicate the hard copy data collection forms;
- Data entry editing followed by more comprehensive editing of data at the DCC;
- A streamlined approach for correction of errors in data and audit trails to document data change transactions;
- Monitoring of timely entry of data by GCC staff and timely resolutions of data discrepancies;
- Regular conference calls between the DCC project managers and the GCC study coordinators to review progress and to address questions and concerns;
- Routine random selection of keyed records for 100% verification
- Periodic visits to GCCs by the DCC and other study staff to review operations; and
- Final check on data quality and completeness as part of the process of making final data files for analysis. In addition to the interactive data edits done during the data entry process, computer programs check that all forms and samples have been received for each participant, and that the data are consistent across the various forms.

6.2 Protocol Education, Training and Certification

To ensure consistent and standardized data collection across the eight GCCs, RTI has developed and implemented a training program for the site coordinators based on the training manual and manual of operations. This training reviews the detailed instructions on subject enrollment and consent, study procedures, data collection, data management procedures, and procedures for specimen collection, processing and shipping. Coordinators are also certified in the requirements for packaging biospecimens and offering them for transport by air according to the International Air Transport Association (IATA) and the U.S. Code of Federal Regulations (CFR).

Various scenarios are utilized to evaluate each site coordinator's understanding of:

- Purpose of study
- Enrollment criteria (inclusion/exclusion)
- Strategies for outreach, consent, and enrollment
- Successful completion and editing of hardcopy forms including successful use of Question-by-Question specifications and recitation of key data elements on all forms
- Review and understanding of the data entry system and the data management system
- Privacy and data security policies
- Demonstrated ability to collect family history and pedigree data

- Demonstrated ability to correctly abstract information from medical records
- Biospecimen collection, processing, packing and shipping within regulations governed by CFR Title 49 and the IATA Dangerous Goods Regulations (DGR)
- Successful completion of course for packaging and shipping dangerous goods
- Willingness to communicate with the DCC
- Willingness to promptly complete and enter data forms
- Willingness to meet target enrollment numbers

Successful completion of the scenarios contribute to the certification procedures for the site. Certification is necessary in order to begin or continue data collection, and is repeated if there are changes to the protocol or data collection procedures. DCC staff make at least annual site visit to each GCC to review the procedures and certification requirements.

In addition to training on data collection procedures, the RTI Biospecimen Manager trains the GCC staff responsible for biospecimen collection, processing, and transport in standardized procedures. GCC personnel responsible for packaging and shipping of the biospecimens to the NHLBI Repository are trained in the CFR Title 49 and the IATA Dangerous Goods Regulations. After the first training session, additional training is available as needed, either to supplement the initial training, train new personnel, or retrain staff members showing difficulties with assignments. RTI documented the steps clearly and concisely in a Specimen Chart that graphically presents the specimen plan from collection through storage, including labeling, quantities and storage distribution. This chart, accompanied by standardized protocols, forms the basis for the biospecimen procedures manual.

6.3 Routine Study and Data Quality Checks

Quality control checks are programmed into the web-based entry system. Checks for internal consistency with respect to dates, acceptable ranges, required items, and skip patterns are established and validated at the time of data entry. In batch, the data undergo additional automated, electronic edits that cannot be included efficiently in the data entry screens, such as cross-form editing.

Edit checks that are performed in real time are replicated by the DCC in batch. In addition, complex within-form and across-form consistency and logic checks are applied at the DCC. These checks are based upon the specifications appropriate to each of the data collection forms. Any failures are reported to the GCC enrolling the patient electronically as error resolution reports. GCC personnel enter the corrections for the keyed data into the electronic file, and an audit trail of corrections is t maintained. This audit trail is transmitted to the DCC with the keyed database. Error resolutions are completed online via the data entry system or externally, using an MS Excel file format to protect the data at the level required by the GenTAC contract.[1]

6.4 Monitoring Reports

To monitor enrollment, data flow, delinquent data, and data quality, reports are generated. These are distributed at least quarterly to GCC staff and the Steering Committee. Annual summary reports are sent to the OSMB. These reports show the number of patients enrolled by condition at each GCC, as well as the number and type of forms received by the DCC, the number of delinquent forms, the number and type of biologic samples sent to the

[1] Note - The only consideration when planning this type of edit system is the need to store the data outside the protective firewall so that it could be accessed at time of edit. In some instances, extreme confidentiality concerns may override the efficiency of such a system.

repository, and the number of unresolved data edits. The DCC collaborates with the study coordinators and investigators to design reports that are meaningful and assist in monitoring the conduct of the study and producing high quality data for analysis.

6.5 Site Visits

The DCC conducts annual site visits to each GCC to monitor adherence to protocol procedures on site. More frequent site visits are made as necessary to provide training to new staff or to retrain existing staff in new or old procedures. Site visits are performed as needed by the data center, NHLBI Project Officer, and a research coordinator in order to ensure data quality, fulfill regulatory responsibilities, and evaluate the performance of investigators and staff. An agenda for these visits is developed by the DCC, the NHLBI, and the GCC. A standardized chart audit; inspection of facilities, personnel, and records; and organizational review is also performed. On behalf of NHLBI, the DCC distributes written site visit results to the GCC principal investigator and coordinator, including: acknowledgement of adherence, any noted or demonstrated specific excellence or proficiency, and/or suggestions for improvement.

6.6 Storage of Case Report Forms and Study Reports

All hard copy study records and the link between the patient name and the subject ID are kept at the GCCs in locked filing cabinets with access limited to authorized study personnel. Each GCC has a unique login and password to enter the secure web-based application for data entry.

6.7 Electronic Data Security

A comprehensive set of IT security measures are applied to all data collection, processing, storage, analysis, and reporting systems according to the contract requirements. These controls are appropriate for the Level 2 security described in the DHHS Matrix of Minimum Security Safeguards (i.e., NIST Moderate). All security controls are discussed in detail in the project specific IT Systems Security Plan (ISSP) submitted by the DCC to NHLBI.

Briefly, all GenTAC data that have not been de-identified must be kept within a Level 2 environment. The DCC maintains this environment behind their firewall. Furthermore, a secure, gated data entry application meeting Level 2 requirements is available to the coordinators through the project website. Coordinators are supplied with tokens by the DCC which allow access to the restricted area for data entry and report generation of identifiable data or personal health information.

7.0 Registry Funding

7.1 Management of the Budget

In providing DCC support to the NHLBI, RTI is responsible for the successful implementation of multiple activities involving numerous participants and organizations. The DCC implements a cost and performance management system to ensure that the contract meets Registry milestones within the contract budget. To achieve this, the DCC team utilizes established RTI systems to:

- closely monitor expenditures and develop realistic cost projections and generate accurate and timely reports
- monitor RTI and subcontractor performance of the work throughout the life of the contract through quality assurance reviews.

Funding is received and managed on an annual basis. Unspent funds in any contract year cannot be rolled over to the next year.

The DCC team uses the internal accounting system to monitor expenditures to the contract and a fiscal management tool to generate projected costs for the contract. These cost monitoring tools, which are required internally for all RTI contracts, are updated at least monthly with current and projected expenditures.

7.1.1 Internal Accounting System

The DCC PI has overall responsibility for implementing and maintaining the budget monitoring system for the project, as well as for the overall fiscal management of the project. As the work progresses, the PI is responsible for monitoring labor and other costs. The accounting system produces a variety of cost reports for specific studies and other specified tasks, including: Project Cost Report, Labor Hours by Employee Report, Other Direct Cost Detail Report, Purchase Commitments Detail Report, Contract Task Summary.

7.1.2 Project Review System

The DCC PI meets quarterly with the RTI Project Management Review Committee to discuss the status of this contract. Project reviews involve a meeting with the project director, project managers, and a review committee comprised of several senior staff members. Topics for review include financial information, including an up-to-date Cost-to-Complete Report, as well as the status of the project, technical schedule, and deliverables. This internal project review provides a means of early identification of potential financial, technical, or schedule issues that may need to be addressed. The Project Management Review Committee also provides guidance and recommendations to the project staff to rectify problem situations.

7.2 Data Coordinating Center Budget

Funding for the DCC is outlined in the contract. The allocated budget is monitored as described above. The DCC PI keeps NHLBI informed as unforeseen issues related to the budget arise and works with them to address these issues in a timely fashion.

7.3 Subcontractor Budgets

The DCC establishes a written subcontract, approved by NHLBI, with each GCC and Core. All invoices from the GCC and Cores are approved by the DCC PI. The subcontractor expenses and performance are monitored on an on-going basis and any issues that arise are discussed with them. However, each subcontractor is responsible for monitoring their own expenses and completing their SOW within their funded amount

As outlined in the RFP, the NHLBI GenTAC Registry base budget includes 10% support for a GCC PI, and up to 150% of a GCC research coordinator, depending on the recruitment target. Research Coordinators spend their time recruiting and enrolling patients, completing the required data forms, retrieving and de-identifying images, and assisting with specimen collection, processing and shipping. Subcontractor travel to Steering Committee meetings is included in their budgets.

8.0 Data Dissemination and Data Sharing Policy

Sharing research data via publications and publicly available resources, such as databases and tissue banks, expedites the translation of research results into knowledge and procedures to improve human health. Data from well-characterized population samples constitute an important scientific resource. It is the view of the NHLBI that their full value can only be realized if they are made available, under appropriate terms and conditions consistent with the informed consent provided by individual participants, in a timely manner to the largest possible number of qualified investigators. The definition of "timely release and sharing" is three years after the completion of the enrollment phase of the study. Ancillary studies conducted concurrently with the registry must also abide by the Data Sharing Policy.

8.1 NHLBI Policy on Preparation of Limited Access Data Sets (LADS)

For contract-supported clinical trials and epidemiology studies, requirements for preparation of limited access data sets have been modified to shorten the timeline and expand the data to be included, as described below. These changes will be effective with contracts awarded on or after October 1, 2005.

Requests for exceptions to these guidelines are considered by the NHLBI if adequately justified. Examples of adequate justification include: unavoidable and unanticipated delays in making data available within the parent study for analysis; presence of provisions in informed consent prohibiting LADS release; evidence of unacceptability of LADS release to communities under study; measurements on too small a subset of participants to be of scientific value. All such requests should be addressed to the Director of the Program Division funding the award.

8.1.1 Introduction

The National Heart, Lung, and Blood Institute (NHLBI) has supported data collection from participants in numerous clinical trials and epidemiologic studies. These data from well-characterized population samples constitute an important scientific resource. It is the view of the NHLBI that their full value can only be realized if they are made available, under appropriate terms and conditions consistent with the informed consent provided by individual participants, in a timely manner to the largest possible number of qualified investigators.

Under no circumstances will data relating to an individual be distributed in any way that is inconsistent with his or her informed consent. Data sets without an informed consent permitting use by non-study researchers are only released if the requester's IRB has approved a waiver of informed consent based on minimal risk to the participants.

Data sets distributed under this policy include only “limited access data”, i.e., records with personal identifiers and other variables that might enable individual participants to be identified, such as outliers, dates, and study sites, removed or otherwise modified. Because it may still be possible to combine the limited access data with other publicly available data and thereby determine with reasonable certainty the identity of individual participants, these data sets are not truly anonymous. They are, therefore, only provided to investigators who agree in advance to adhere to established policies for distribution.

Limited access data sets are available for NHLBI studies supported by contract and for selected studies supported by cooperative agreements or other grants. However, data are not being provided for limited access if the Institute deems them to be unreliable or invalid. All proposed data exclusions must be strongly justified and whether proposed by the study investigators or Institute staff, each one must be reviewed and approved by the director of the NHLBI program division that sponsored the study.

8.1.2 Definitions

- ***Data*** - Information collected and recorded from subjects enrolled in the study through periodic examinations and follow-up contacts, not to include original specimens or images.
- ***Commercial purpose*** - Data is considered as being for a commercial purpose if they are to be used by an investigator who is an employee of a for-profit organization, if they are to be used by an investigator to satisfy a contractual relationship with a for-profit organization, or if they are to be used by an investigator as the basis for a consulting relationship with a for-profit organization. Data is also be considered as being for a commercial purpose if the investigator(s) take any affirmative steps to facilitate commercial use of results derived from the data.
- ***Non-Commercial Purpose Data Set*** – A data set consisting of all records except those for study subjects who requested that their data not be shared beyond the initial study investigators.
- ***Commercial Purpose Data Set*** – A data set consisting of all records except those for study subjects who requested that their data not be shared beyond the initial study investigators or used for commercial purposes.
- ***Non-Commercial Purpose Pedigree/Genetic Data Set*** – A pedigree/genetic data set consisting of all pedigree and genetic data except those for study subjects who requested that their data not be shared beyond the initial study investigators.
- ***Commercial Purpose Pedigree/Genetic Data Set*** – A pedigree/genetic data set consisting of all pedigree and genetic data except those for study subjects who requested that their data not be shared beyond the initial study investigators or used for commercial purposes.

8.1.3 Data Set Requests

Responsibilities of Investigators Seeking Access to Study Data

To ensure that the confidentiality and privacy of study participants are protected, all investigators seeking access to data from NHLBI-supported studies that are in the possession of the Institute must execute and submit with their requests a GenTAC Data Use Agreement (DUA) form (**Appendix A**). Because of the potential for identification of individual study subjects and consistent with the conditions included in the DUA, investigators seeking access to study data must also submit an approval from their Institutional Review Board (IRB). An expedited review from the IRB is acceptable.

Unless a specific request for the Non-Commercial Purpose Data Set is received, investigators requesting access to study data are provided with the Commercial Purpose Data Set. Investigators seeking access to the Non-Commercial Purpose Data Set must submit a signed statement affirming that they will not be using the data for a commercial purpose as defined above. Investigators who do so must recognize that if they subsequently develop results of potential commercial value, they will have to replicate those results using the Commercial Purpose Data Set before they can take any affirmative steps to facilitate commercial use of the results.

Investigators interested in receiving a Pedigree/Genetic Data Set must specifically request it. Investigators seeking access to a Pedigree/Genetic Data Set must describe the specific need for access to it in the Research Project description of their signed Data Use Agreement. Investigators using these data sets are strongly discouraged from publishing

individual pedigree structures and are prohibited from investigation into issues such as non-paternity.

Investigators should recognize that they are bound by the conditions of the GenTAC DUA. Failure to comply with it could result in denial of further access to NHLBI data sets. Moreover, violation of the confidentiality requirements in a Data Use Agreement may lead to legal action against the recipients of the data by study participants, their families, or the U.S. Government

Responsibilities of Study Investigators in Preparing Data Sets

Investigators in NHLBI studies covered by this policy are required as part of the terms and conditions of their awards to prepare and deliver to the NHLBI limited access data sets that satisfy NHLBI requirements. Included among them are documentation, elimination of personal identifiers, and modification of other data elements so as to reduce the likelihood that any individual participant can be identified.

Two limited access data sets, i.e., a Non-Commercial Purpose Data Set and a Commercial Purpose Data Set, and, if applicable, two pedigree/genetic data sets, i.e., a Non-Commercial Purpose Pedigree/Genetic Data Set and a Commercial Purpose Pedigree/Genetic Data Set, and associated documentation, must be provided in electronic form to the Institute. In addition, investigators must provide the Institute with two separate lists of participant identification numbers, one consisting of those participants who asked that their data not to be shared beyond the initial study investigators and the other of those participants who asked that their data not be used for commercial purposes.

Investigators in ancillary studies based on ongoing (parent) studies that are required by this policy to produce limited access data sets must submit ancillary study data to the NHLBI through the parent study Coordinating Center or limited access data submission process established by the parent study. Ancillary studies conducted on small subsets of a study sample may be appropriate for exclusion from limited access data sets; requests for their exclusion should be justified and addressed as described in the Introduction above.

- **Documentation** – Documentation for limited access data sets must be comprehensive and sufficiently clear to enable investigators who are not familiar with a data set to use it. The documentation must include data collection forms, study procedures and protocols, descriptions of all variable recoding performed, and a list of major study publications.

  In addition, a summary documentation file, usually called a "readme" file, is required. It must provide a complete overview of the data and a description of their use for investigators who are not familiar with the data set. It must also contain a brief description of the study (including a general orientation to the study, its components, and its examination and follow-up timeline), a listing of all limited access files being provided, a description of system requirements, a generation program code for installing a SAS file from the SAS export data file, and a frequency distribution for selected key variables.

- ***Data Storage and Format*** – The data are to be stored on a CD ROM unless the investigators and the NHLBI mutually agree upon an alternative storage medium. Both the comprehensive documentation and the summary documentation must be prepared in a consistent format, either as a Word Perfect, MS Word, ASCII, or portable document format (PDF) file and included on the same storage medium as the limited access data set. To ensure access by users with disabilities, all PDF files must be created in Adobe Acrobat version 5.0 or higher. Documentation that is not available in electronic form, such as data collection forms, should be scanned into a graphics file, converted to a PDF file using Adobe Acrobat version 5.0 or higher, and saved on the same medium as

the data set. Pedigree data should be provided in a format readable by standard genetic analysis programs such as SAGE and SOLAR, with one individual's data per line beginning with pedigree identifier, individual's id, father's id, mother's id, and individual's sex.

  - *Content of Limited Access Data* – In addition to summary information, limited access data sets also include for each study subject those raw data elements that have not otherwise been processed into summary information. For Observational Epidemiology Studies like GenTAC, these data include all of the examination data obtained in each examination cycle, ancillary data, and/or all of the follow-up information available up to the last follow-up cycle cutoff date

- ***Timing of Release of Limited Access Data***

  - Observational Epidemiology Studies – Epidemiology studies typically have an examination component and a mortality/morbidity follow-up component. Data from each cycle of an examination or follow-up component are prepared by the study coordinating center and sent to the NHLBI for distribution as a limited access data set no later than 3 years after the completion of each examination or follow-up cycle or 2 years after the baseline, follow-up, genetic, ancillary study, or other data set is finalized within the study for analysis for use in publication, whichever comes first.

  - Ancillary Studies – In those cases in which the timeline for an ancillary study differs from that of its parent study, the release date relates to the timeline of the ancillary study.

8.1.4 Procedures for Protection of Privacy for Limited Access Data Sets

Institute Review and Approval of Limited Access Preparation

The NHLBI requires that the data be provided in a manner that protects the privacy of study subjects. The Institute requires appropriate documentation of the steps taken to protect their privacy in preparing a limited access data set. A summary of all proposed modifications and deletions to be made to a data set in preparing it for limited access must be submitted to and approved by the director of the division that sponsored the study prior to their implementation.

Guidelines for Limited Access Preparation

The following guidelines provide a framework for decision-making regarding preparation of limited access data sets:

- All data for study subjects who refused to permit sharing their data with other researchers must be deleted from the Non-Commercial Purpose Data Set.
- All data for study subjects who only refused to permit sharing their data for commercial purposes must also be deleted from the Commercial Purpose Data Set.
- Study subject identifiers:
- Obvious identifiers (e.g., name) must be deleted.
- New identification numbers must replace original identification numbers. Codes linking the new and original data should be sent to the NHLBI in a separate file, not included on the CD ROM, so that linkage may be made if necessary for future research.
- Variables that might lead to the identification of study subjects and participating clinical centers in multicenter studies, or variables that are sensitive, inaccurate, or of limited scientific utility:

- Clinical center identifier -- In studies that have centers with a large number of subjects per center, the data may offer little possibility of identifying individuals. For them, the investigators and the NHLBI determines whether to include them on a case-by-case basis.
- Interviewer or technician identification numbers must be recoded or deleted.
- Sensitive data, including illicit drug use, risky behaviors, sexual behaviors, and selected medical conditions (e.g., alcoholism, HIV/AIDS) must be deleted.
- Regional variables with little or no variation within a center because they could be used to identify that center must be deleted
- Unedited, verbatim responses that are stored as text data (e.g., specified in "other" category) must be deleted
- Pedigree and genetic data are distributed in separate data sets only to investigators specifically requesting them. Genotyping data for any person in whom potential pedigree errors are detected must be deleted.
- Dates: All dates should be coded relative to a specific reference point (e.g., date of study entry). This provides privacy protection for individuals known to be in a study who are known to have had some significant event (e.g., a myocardial infarction) on a particular date.
- Variables with low frequencies for some values, that might be used to identify participants, may be recoded. These might include:
    - Socioeconomic and demographic data (e.g., marital status, income, education, language).
    - Household and family composition (e.g., number in household, number of siblings or children, ages of children, number of brothers and sisters, relationships in study).
    - Numbers of pregnancies, births, or multiple children within a birth.
    - Anthropometry measures (e.g., height, weight, waist girth, hip girth, body mass index).
    - Physical characteristics (e.g., missing limbs).
    - Detailed medication, hospitalization, and cause of death codes, especially those related to sensitive medical conditions as listed above, such as psychiatric disorders.
    - Prior medical conditions with low frequency (e.g., group specific cancers into broader categories) and related questions such as age at diagnosis and current status
    - Parent and sibling medical history (e.g., parents' ages at death).
- Race/ethnicity and sex information when very few participants are in certain groups or cells.
- Polychotomous variables: values or groups should be collapsed so as to ensure a minimum number of participants (e.g., at least 20) for each value within each race-sex cell.

- Continuous variables: distributions should be truncated if needed to ensure that a minimum number of participants (e.g., at least 20) have the same highest and lowest values in each race-sex cell.
- Dichotomous variables: data should either be grouped with other related variables so as to ensure a minimum number of participants (e.g., at least 20) in each race-sex cell or deleted

- The investigators may realize that other variables may make it easy to identify individuals. All such variables should be recoded or removed. The NHLBI program officer or project administrator should be consulted concerning such variables.

8.2 GenTAC Data Dissemination Plan

A data dissemination plan will be developed by the DCC to document the data obtained in the Registry that may lead to a better understanding of how to manage and treat patients with aortic aneurysms and other cardiovascular complications associated with connective tissue diseases. The data available for distribution includes a limited access dataset of de-identified patient data, prepared in accordance with the NHLBI Limited Access Data Clause, accompanying data documentation, and stored biologic specimens labeled with code numbers. Results from the registry are disseminated through submission of manuscripts for publication in the scientific literature and presentations at national meetings. All publications resulting from GenTAC data must acknowledge the NHLBI as a source of funding.

8.3 GenTAC Data Sharing Policy

The primary goal of the GenTAC Registry is to establish a data and biospecimen inventory that will be shared with Registry investigators and qualified researchers outside the Registry interested in studying aspects of genetically induced thoracic aortic aneurysms that are not being addressed by study investigators. De-identified patient-level data and biological specimens are made available to researchers within and outside the Registry through an application and approval process as part of the study's Data Dissemination Plan. To protect the confidentiality and privacy of the subjects, outside investigators granted access to the limited access data and biologic specimens must adhere to strict requirements incorporated into a standard Data Use Agreement. In accordance with NHLBI policy, outside researchers are also required to submit an approval from their Institutional Review Board (IRB). Investigators within the Registry are granted access to existing de-identified data through their current IRB approval.

Information on the types and quantities of biological specimens available to investigators is shared according to the “Guidelines for Human Tissue Repository,” in which NHLBI provides specific guidelines for applying, reviewing, and processing requests for biospecimens collected through the Institute’s contracts. These guidelines include Specimen Request for Performance of Collaborative or Ancillary Studies, Materials Transfer Agreements, and Restricted Use of Specimens. Testing that is done by an investigator outside the Registry as part of an ancillary study is not shared with the study subjects.

A formal policy for release of data will be developed by the Steering Committee. Guidelines for the Data Sharing and Distribution Policy will include the following:

- The contract is governed by the policy
- A limited data (de-identified) set is prepared to make resource available to qualified investigator for research or commercial use.
- Informed consent will be layered to permit use of data by non-primary investigators including a right to opt out for each layer. The informed consent will also recognize that patients can ask not to be notified of incidental research information.

- Genetic data sets are more difficult if not impossible to render completely anonymous.
- Since this is an exploratory study, a statement of limited clinical utility of data for individual patients will be underscored in the consent form.
- Removal of information not relevant to primary research objectives will be balanced to protect confidentiality while maintaining relationships that may be of value to the primary study objectives.
- The primary investigators will develop rules/procedures for “ancillary studies”. That is during the active phase of the registry, additional protocols making use of GenTAC data or infrastructure are encouraged but should follow the process developed by the primary investigators.
- RTI maintains a de-identified data set using a random ID number. The ability to link study ID to individual patients is maintained at the GCC in the event that individual patient (or circumstance) requests or requires information.
- Informed consent documents must meet IRB requirements and must be layered including an opt out for each layer.

8.4 Use of Resources by GenTAC and Non-GenTAC Investigators

A key strategy for achieving GenTAC’s scientific goals is that data and information collected by and generated by GenTAC investigators become broadly available. As a condition of using GenTAC data, all investigators with approved proposals must agree to conduct experiments consistent with GenTAC’s aims, study consent, and data use agreement.

8.4.1 Embargo Period for Exclusive Use of Genetic Data

All genetic data generated from GenTAC samples must be submitted to the DCC for deposition in the GenTAC genetic database within one year of the date of completion of the genetic analyses. If additional time is required to protect the data prior to publication the investigators will contact GenTAC and request additional data embargo time. Investigators have exclusive rights to publish the analysis of their genetic data before it becomes available to others. The investigator will be contacted before genetic data is released to other investigators if GenTAC has not been informed that the study is completed. If investigators determine that the data will address a new question, they will inform GenTAC through submission of a research proposal thereby requesting permission for expanded use of the data. Investigators using NIH funds to generate the genetic data are required to follow all NIH policies regarding access to genetic data. Use of the GenTAC resource constitutes use of NIH funds as it is a NIH sponsored registry.

The embargo period for exclusive use of genetic data generated from GenTAC samples is one year from receipt of the last shipment of GenTAC biospecimens sent as part of the approved research project. At this time, all genetic data generated as part of the approved project must be sent to GenTAC for deposit into the genetics database and available to others. An extension to this deadline can be requested in writing, which will be reviewed by the Genetics Subcommittee for approval.

8.4.2 Acknowledging GenTAC in Publications

Publications of research that use GenTAC data should cite GenTAC using the following acknowledgement:

NHLBI National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) supported under contract HHSN268200648199C/ADB N01-HV-68199 with RTI International.

The dissemination of results and information to the public will be done according to each institution's publication policy and published NIH guidelines for dissemination of research results (http://grants.nih.gov/grants/policy/nihgps_2001/part_iia_6.htm).

9.0 Concepts and Ancillary Studies Policy

9.1 Introduction

A concept is a proposal funded by the DCC to conduct an analysis of existing data and that addresses a research question included in the GenTAC protocol or otherwise part of the planned goals of the registry. An ancillary study is one that derives financial support from the DCC or from sources other than the GenTAC contract. Examples include studies funded by investigator-initiated NIH research awards (R01s), grants from academic institutions, private sources (e.g., drug companies), or those performed without external funding (generally because of the special interest of a researcher). GenTAC investigators are encouraged to consider concepts and ancillary studies and to involve other investigators within or outside of their institutions in this process. Ancillary study proposals are also considered from non-GenTAC investigators and institutions.

There are three distinct categories of proposals.

Category I includes all concepts and ancillary studies that propose to make use of existing GenTAC resources, including data and biospecimens that are already archived at the data coordinating center (DCC) or are being collected by the GenTAC clinical centers (GCCs) as part of the GenTAC mission. For review purposes, this category is divided into two subcategories:

Ia: requests the use of existing de-identified GenTAC data only

Ib: requests the use of existing GenTAC specimens and data

Category II includes any ancillary study that 1) requires additional data and/or biospecimen collection, and 2) will be supported by GenTAC.

Category III includes any ancillary study that 1) requires additional data and/or biospecimen collection, and 2) includes outside funding or a request to a source for outside funding. These proposals are not supported financially by GenTAC. Proposals in this category may apply for preliminary approval if it is needed in order to apply for the funding. Full approval will need to be obtained once the funding is secure.

Category II and III may involve re-contacting study subjects to collect additional information, follow-up data, and/or additional biospecimens. The expanded protocol may include one or more of the GCCs, depending on the resources requested. In some cases, Category II and III proposals will require additional IRB review.

All genetic data generated from GenTAC samples will be deposited in a GenTAC Genetics database for use by other investigators. This requirement is included on the application form. Investigators generating genetic data must submit them to the DCC within one year of receiving the last shipment of GenTAC biospecimens. An extension to this deadline may be requested in writing, which will be reviewed by the Genetics Subcommittee for approval. The investigator generating the genetic data from GenTAC samples is responsible for submitting the results to dbGaP.

9.2 Scientific Advisory Board

The Scientific Advisory Board (SAB) consists of three members of the external research community that have been appointed to facilitate strategic planning and to advance the science

and use of the GenTAC registry resources. They are also responsible for providing unbiased and objective review of all research proposals from internal and external investigators, writing critiques of the proposals, and providing recommendations to the Operations Committee.

9.3 Development and Submission

An individual who develops a concept or ancillary study may be a Registry principal investigator, an alternate, or an individual external to GenTAC. When planning an ancillary study, the applicant should consider availability of the study population and the funding source. Funding for ancillary studies may come from the DCC or from sources outside of GenTAC. Applicants developing a concept or ancillary study should consult the DCC as they develop their studies. They may also want to consult with an investigator of a previously approved proposal if they want advice about a successful submission.

Concepts and ancillary studies should be submitted to the DCC on the approved Research Proposal Application Form (Appendix B) found under the "For Researchers" section of the GenTAC public website. Completed forms should be submitted via email per the instructions on the form. Required elements of a completed package include:

- Application form
- Biosketch of PI and other significant co-investigators
- IRB approval letter, if applicable

A Materials Transfer Agreement may also be required after a proposal that requests specimens has been approved.

9.4 Review Process

Initial Review Phase

At least 2 months before any deadlines (e.g., abstract due dates), or longer if an NIH grant is being prepared, the applicant should send the completed concept form to the DCC for review for completeness of the required elements and to ensure that the data and resources are available to support the request. At this time a tracking number starting with "GEN" is assigned to the proposal. In addition, if there are any questions or clarifications, the DCC works with the investigator to address them before sending the proposal to the Operations Committee (OC) for preliminary review.

The OC reviews the proposal based on the following elements and discusses the application on their next weekly conference call:

1. The application is complete and all application sections have been addressed
2. The study should not interfere with other parts of the GenTAC protocol.
3. Availability of the proposed study population and requested samples must be confirmed by the DCC.
4. The study must not have significant overlap with proposed or on-going studies by GenTAC investigators, nor can it significantly deplete resources needed by GenTAC studies (*i.e.* DNA, tissues).
5. The study must not hamper continued participation of study subjects in the registry.
6. The study does not place an undue burden on the DCC and the GCCs.
7. The timeline for completion is reasonable
8. The end-product should include a presentation or published manuscript of the results
9. Requested or available funds must be adequate to support the proposed study. Category III studies seeking full approval must provide documentation of sufficient resources to support the expanded GenTAC activities as well as the proposed study.

10. Individual GCCs may decline participation in a Category II or III studies.

If he proposal has all of the required elements, it will follow the appropriate review process outlined below.

Formal Review Phase

Data sharing is a primary goal of GenTAC II and the goal is to accept as many **meritorious** proposals as possible. Research proposals are sent to the SAB for review on a monthly basis unless there is a specific deadline to meet, such as a grant application.

For Category Ia proposals not requesting specimens, the OC is the only level of formal review.

For Category Ib studies requesting biospecimens, in addition to the SAB and the Study Chair, at least two members of the SC is invited to participate as reviewers based on their expertise. The purpose of the additional SC reviewers is to provide another layer of review when non-renewable resources are being requested.

For Category II studies, in addition to the SAB and the Study Chair, at least two members of the SC is invited to participate as reviewers based on their expertise. The purpose of the additional SC reviewers is to provide representation of the expected burden on the GCCs to complete the study and how the additional data collection will affect completion of other GenTAC contract activities.

For Category III studies, in addition to the SAB and the Study Chair, at least two members of the SC are invited to participate as reviewers based on their expertise. The purpose of the additional SC reviewers is to provide representation of the expected burden on the GCCs to complete the study and to assure that additional data collection will not affect completion of other GenTAC contract activities. The DCC and GCCs to be involved in Category III studies may be requested to submit budgets to the study applicant that cover the additional costs for new activities outside the GenTAC budget. DCC involvement is not required, but may be recommended if the study requires assistance with data management. The ancillary study applicant reviews the budget requests and work with the GenTAC subcontractors to negotiate final budgets. Ultimately, the applicant is responsible for incorporating GCC and DCC costs into the study budget to cover any additional costs incurred in the course of the study and to set up non-GenTAC subcontracts with each institution to reimburse for these costs.

Written Critiques. Regardless of the category level of the proposal, a written critique is done by each reviewer and sent to the DCC. The length of the written review is dependent on the goal of communicating to the applicant. SAB may provide more detailed comments if they think the proposal is meritorious and can be improved by addressing the critique. In addition,

- Reviewers may determine that acceptance is contingent on the addition of a more experienced investigator.
- If the proposal addresses an idea already under consideration by a GenTAC investigator, the reviewers may determine that acceptance is contingent upon collaboration with that investigator.

Recommended Revisions. One common outcome of the review process is that the applicant is asked to revise their proposal based on the reviewer critiques or otherwise separately address the weaknesses identified. The SAB is aware of the importance of utilizing the GenTAC resources and the significant investment of time that investigators have devoted to conducting their research projects. The goal of the SAB is to approve as many scientifically meritorious applications as possible without overburdening the DCC or the study subjects.

If a project is considered scientifically high risk by the SAB and requests biospecimens, the recommendation for approval may be based on approving a pilot study on a limited number of specimens, such as DNA obtained from only whole blood and not from saliva (where the DNA is non-renewable).

Approval Process. If the reviewers recommend approval by a majority vote, the DCC sends an approval notice to the investigator and work with them to provide the necessary data and analyses. The DCC also notifies the full SC of research proposal approval, posts a summary of the proposed study on the GenTAC website and places the proposal number on the tracking sheet which documents progress of each proposal and their end results. Each proposal that disseminates data or results that were generated with GenTAC resources must acknowledge the GenTAC contract information as a source of funding. This information is included on the application form.

10.0 Publications and Presentations Policy

The Publications Committee is charged with final review and approval of all manuscripts and abstracts prior to submission. This is a 13 member committee consisting of the principal investigators from the eight clinical centers, the imaging core, the phenotyping core, the Data Coordinating Center (DCC), NHLBI and the Steering Committee (SC) Chair. The goal of this committee is to ensure submission of high quality manuscripts and appropriate authorship credit.

The purpose of the publication policy is to:

- Encourage the timely preparation of high quality publications and presentations from GenTAC investigators.
- Provide appropriate academic recognition to participants who make significant and substantial contributions to the GenTAC Registry.

10.1 Single Research Unit versus Cross-unit Publications and Presentations

The registry is expected to produce numerous publications and presentations. It is possible that selected publications or presentations involve activities specific to a single GCC, while others will involve more than one GCC. Any publication or presentation of work that utilized GenTAC data or specimens is governed by the rules set forth below. If there are any ambiguous situations, then the issue should be considered by the GenTAC Publications Committee before manuscript or abstract submission.

10.2 Presentations

Any abstract submitted for presentation must be sent to the DCC PI no later than two weeks before it is due to the conference offices. (Unusual circumstance requiring shorter time frames are reviewed on a case by case basis.) The DCC PI circulates the abstract to all members of the Committee with a note saying that the investigator has 5 days to return objections or it is assumed that the abstract is acceptable.

10.3 Establishing Authorship

Decisions about who appears as a listed author on a publication can be complex when the work upon which the publication is based has been the result of collaboration by a large number of individuals. Persons who have taken part in the actual writing of a paper or preparation of a presentation generally appear as the first authors. Additional authorship is something that must be worked out by the lead author/investigator responsible for the concept which was the basis for the paper.

The following list is offered as a guideline. Any of these items can be modified in consultation with the Publications Committee in the context of an individual submission:

- To foster collaboration between researchers and motivate all levels of staff involved in the Registry, a general governing principle is to recognize as many persons as sensible on a paper or presentation. For the sake of practicality, distinctions must be made between recognition and authorship. In addition, the authors on an abstract may be more concise than those on the subsequent manuscript, but followed by "for the GenTAC Registry Consortium".
- Be familiar with the journal being targeted as a publication source so that the policy on authorship is clear from the start and the appropriate number of authors is assigned based on journal limitations.
- If a publication or presentation involves data primarily related to one site, the principal investigator from that site and the lead author (if different) should determine the authors, following journal policy and the plan for developing the manuscript.
- If a publication or presentation makes use of data collected from all or most of the Registry sites, at least one person from each site should be named as an author. The principal investigator from each site can choose the specific person to be listed. Depending on the impact of the results presented in such a publication, the primary author may decide to list all GenTAC investigators from all sites. Ideally, this decision should be made in advance of submission of a final paper to the Publications Committee. However, during review, the members of the Committee may assess the presented information as particularly important and make a recommendation to expand the authorship.
- If a paper is related to an area of particular investigator expertise, that investigator should assist with manuscript preparation and be included as an author.
- For papers using exclusively GenTAC data or specimens, the GenTAC Registry Consortium should be listed as one of the authors, preferably the last author. However, in some cases there may be a more appropriate senior author. The list and order of authors is at the discretion of the lead and senior authors. A full list of current consortium members should be included in the Appendix of the submitted paper and is available from the DCC. The list includes names, title and organizational names and insures that listings are consistently handled across all Registry publications.
- For papers using GenTAC data or specimens in addition to data from other studies or cohorts, the GenTAC Registry Consortium or the PIs of the corresponding centers where the data came from may be included as co-authors if appropriate, depending on their scientific contribution of the work.
- To avoid confusion and resulting disputes about authorship in the later stages of preparation, early discussion about authorship is suggested and consultation with the Publications Committee is recommended.

Investigators from all GenTAC groups are encouraged to participate in study-related publications.

10.3.1 Authorship Decisions

Authorship should be openly discussed and authors selected as soon as responsibilities are assigned for the preparation of a report or paper. Having agreed on the key objectives, the research collaborators should evaluate the criteria of authorship and make preliminary

decisions. These decisions may need to be revised based on actual contributions to the report or paper. In most cases, final authorship should be decided after completion of the first draft.

The primary author should be chosen through negotiations among participants on or before writing the first draft, based on the requirements of primary authorship.

10.3.2 Disputes in Authorship

The collaborators in a study should first discuss disagreements about authorship. The authors should review the criteria for authorship during such discussions. If disputes still exist, the matter may be taken to the Publications Committee (i.e., the voting members of the SC). The resolution should be based on the above guidelines and any authorship guidelines that exist for the particular client or outside collaborators. Unresolved disputes concerning authorship should be referred to the Steering Committee Chair for final decision.

10.3.3 Acknowledgements of Other Contributors

Authors should acknowledge the contributors whose participation is not substantive enough to warrant authorship. A contribution to one of the areas of authorship (for example, advisorship, data collection, or review of study) is not sufficient for authorship but should be mentioned in the acknowledgements.

10.3.4 Acknowledgements of Funding Source

The NIH expects that press releases, presentations and publications emerging from the GenTAC Registry or using GenTAC resources (data or specimens) acknowledge the funding sources provided by NIH and other groups as appropriate and acknowledge the source of the data as being from the GenTAC Registry. **The following statement should be included in all press releases and manuscripts submitted for publication:**

> The GenTAC Registry has been supported in total by US Federal Government contracts HHSN268200648199C and HHSN268201000048C from the National Heart Lung and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Bethesda, MD).

10.4 Review Process

The Publications Committee reviews draft publications with the following objectives in mind:

- to prepare comments to assist collaborating scientists to publish papers of the highest quality;
- to correct factual and conceptual inaccuracies;
- to safeguard the rights of volunteer subjects; and
- to inform the NHLBI and OSMB of all public dissemination of information.

Authors should plan to distribute at least two rounds of the draft manuscript to the Publications Committee before it is considered final. Authors should incorporate as many of the reviewer's comments as possible, especially if they are from co-authors. The lead author has the final authority regarding when the manuscript is considered final and ready for submission. The final version of the manuscript is sent to the DCC and the co-authors for the files. The DCC sends the final version to the NHLBI as part of the contract deliverables.

10.4.1 Papers

Draft manuscripts should be sent to the DCC PI at least three weeks before the intended submission date. The paper submitted for final review should be in a final form (title, abstract,

tables, references) required by the journal to which they are being submitted. The journal to which the manuscript will be submitted should be indicated.

Members of the Publications Committee should return their comments to the lead author within two weeks; no response will indicate concurrence with the submission. It is hoped that a consensus will be reached among the reviewers regarding the final text. If there is disagreement among the members of the GenTAC Publications Committee, the Study Chair identifies at least two reviewers from among senior investigators and verifies their availability for reviewing the document. The reviewers are chosen for their expertise in the subject matter of the particular document and for their understanding of the study as a whole. Each reviewer is asked to judge whether or not the publication as written will affect the study's process, its acceptance, or the interpretation of its results. If the reviewers agree that the document is not scientifically rigorous, the manuscript is returned to the lead author with suggestions for appropriate changes.

10.4.2 Public Presentations

NHLBI is very interested in having publications and presentations made by members of the Steering Committee as rapidly as possible in order to have visibility in the international scientific community. Therefore the Steering Committee should proactively identify the major meetings where it would be appropriate to have a presentation and identify someone who usually attends that meeting to make a presentation. The DCC is available to assist with preparing presentations or providing slides describing GenTAC background, procedures and data.

10.4.3 Interviews and Press Releases

An interview is any discussion with a member of the press, a science writer or radio or television commentator that in turn provides information for public dissemination. Press releases and interviews must acknowledge that the registry is funded by the NHLBI and NIAMS and include the contract numbers (see Section 10.3.4). In addition, the following specifications should be followed.

If a GCC or DCC investigator is solicited for a press release or interview, it may be given without prior review and approval by the Steering Committee, provided the substantive content is limited to information available in the final protocol or the Manual of Operations, with no added interpretation or inferences. Should a collaborating center be solicited for information other than that detailed above, the center should refer the soliciting party to the Study Chair.

NHLBI disseminates GenTAC activities by linking GenTAC related press releases and interviews to the NHLBI Public website. Thus GCC or DCC investigators are expected to inform NHLBI through the DCC when they are giving an interview or a press release.

APPENDIX A

DATA USE AGREEMENT

GenTAC Registry - DATA USE AGREEMENT

Information obtained from a subject or participant during the conduct of research is confidential and is collected with the intent that it be used only for statistical reporting or research purposes. Therefore, it is necessary to insure, to the fullest extent possible, that any use of such data be limited to research by legitimate investigators, and in accordance with applicable national and international laws and this Data Use Agreement (DUA). Use of such data for any other reason, particularly those resulting in the disclosure of personal information, will be prosecuted to the fullest extent of the law.

Before research data ("Data") can be released to you, you must agree to the following provisions. For the purposes of this DUA, the term "Data" includes both behavioral and biological information (specimens) collected or any derivatives thereof, including copies, summaries, subsets, and compilations of the Data or aliquots and test results obtained from biospecimens. By requesting and receiving Data from RTI International, the Recipient of the Data ("Recipient" or "You") agrees to the following:

1. You certify that the statements made in the Proposal Request Form (previously submitted and approved) are complete and accurate.

2. You agree not to release data obtained under this agreement to any other person. All access to data must be approved via this application process. All data recipients must complete a Data Use Agreement and Proposal Request Form.

3. You agree not to use the Data for purposes other than those described in your request and research plan and as approved by your Institution's IRB.

4. You will establish and maintain the appropriate administrative, technical, and physical safeguards (e.g., use of locked storage facilities, and passwords with a minimum of six characters, including alpha-numeric characters as well as symbols, etc.) to protect the confidentiality of the data and to prevent unauthorized use or access to the Data.

5. If you leave your current employer (institution), you will notify RTI within 30 days regarding the disposition of all copies of the data and return/destruction of biologic specimens and will adhere to RTI's instructions and all applicable IRB guidelines. You may not take any biologic specimens or copies (or partial copies) of the data when you leave.

6. You will not attempt to link, nor permit others to link, the Data, including results from specimens, with individually identified records (e.g., name, detailed demographic information that may identify the individual) in any other database.

7. Neither you nor anyone else having access to these Data will attempt to learn the identity of any of the study participants. In the event that you discover or are able to deduce the identity of a specific participant, you agree not to reveal the information nor attempt to contact the individual(s).

8. You agree not to release any findings or information derived from the Data if such findings contain any combination of data elements that might allow for identification or the deduction of a study participant's identity.

9. You agree to subject any findings or manuscripts proposed for public release (e.g., abstracts, presentations, publications) for review by NHLBI, RTI, the GenTAC Publications Committee, and your institution prior to release to ensure that data confidentiality is maintained, that individual study participants cannot be identified, and to confirm the analysis of the data. You agree to abide by any decisions made by NHLBI, RTI, or the Publications Committee of the GenTAC Registry in regards to changes necessary to assure confidentiality, and will not submit such documents for publication until receiving approval to do so. You agree that approval may be withheld for any reason deemed in violation of this agreement, such as, data presentation that may result in the identification of participants.

10. You will report immediately to RTI any use or disclosure of the Data other than as permitted by this DUA, and will take all reasonable steps to mitigate the effects of such improper use or disclosure, cooperating with all reasonable requests by RTI towards that end.

11. You agree that in the event NHLBI, RTI or the GenTAC Publications Committee determines or has a reasonable belief that you have violated any terms of this agreement, termination of this DUA will occur and you will be required to return the Data and all derivative files. RTI may also seek legal action against you or your Institution to prevent any disclosure of Data by you to any individual or institution not approved to receive the Data. You understand that as a result of this determination or reasonable belief that a violation of this agreement has occurred, RTI may also refuse to release further data to you. In addition, RTI will report any misuse or improper disclosure of Data to the Office of Human Research Protections (OHRP) and any applicable Institutional Review Boards (IRBs), as well as to other authorized entities as required by applicable law.

12. You agree to destroy all copies of Data at or before the expiration date of this DUA or, where directed by RTI, to return such Data or specimens to RTI per its instructions. You will certify such destruction or return by signing and returning to RTI a Certificate of Data Return or Destruction form, provided by RTI.

13. You agree that either party may terminate this agreement upon thirty days written notice. Upon any termination or the expiration of this DUA, Recipient will return or destroy, at RTI's instruction, all copies of Data, derivatives, or portions thereof in its possession.

14. This Agreement shall be construed in accordance with the laws of the State of North Carolina, and in a manner that supports compliance by RTI and Recipient with all applicable requirements of HIPAA (Health Insurance Portability and Accountability Act), the Privacy Rule, and the Privacy Act of 1974.

15. The Terms and Conditions of this DUA are for the sole benefit of RTI and the Recipient and do not create any third party beneficiary rights.

16. Any publication, presentation and report prepared using these data or specimens must acknowledge the GenTAC Registry as follows:

    NHLBI National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) supported under contract HHSN268201000048C/ADB N01-HV-08238 with RTI International.

The following items are required prior to approval of this Data Use Agreement and release of the Data or Specimens. Please indicate if the following items are attached:

_____ A Proposal Request Form describing the data/specimens requested and the research plan.

_____ A copy of the current IRB approval from your Institution for this activity.

_____ A completed and signed Material Transfer Agreement for biospecimen requests.

Signature of Individual Responsible for this Data Request

Your signature indicates that you agree to comply with the above stated provisions. Deliberately making a false statement regarding any matter within the jurisdiction of any department or agency of the United States Federal Government violates 18 USC 1001 and is punishable by a fine or prison.

Name (printed or typed)

Institution/Organization

Address

Telephone No. FAX No.

E-mail address

Signature Date

To be completed by designated staff in RTI's Office of Research Protection and Ethics (ORPE).

National Registry of Genetically Triggered Thoracic Aortic Aneurysms (GenTAC) 0212746

Project Title RTI Project Number

HHSN268201000048C/N01-HV-08238 **NHLBI/NIH**

Contract Number Sponsoring Agency

Barbara L Kroner, PhD

Project Director Name (printed or typed)

Effective Date of this Agreement: _____

Expiration Date of this Agreement (from Item 8 on Data Request Form): _____

Juesta Caddell, PhD, Director

ORPE Staff Name (printed or typed)

ORPE Staff Signature Date

APPENDIX B

RESEARCH PROPOSAL FORM

GENTAC RESEARCH PROPOSAL APPLICATION

Complete this form to describe your proposed research and request use of existing GenTAC data and/or biospecimens. The text boxes will expand as you type. A complete application includes:

- This completed form (no longer than 5 pages, excluding tables and graphs).
- A biosketch for the lead author and any co-investigators to be highlighted.
- IRB approval letter, if applicable
- An MTA may also be required if the concept is approved

Once your application is final, it will take approximately 4-6 weeks for the Scientific Advisory Board (SAB) to provide their recommendation and for the OC to make the final decision.

Return completed application and associated documents to Amanda Lewis-Evans (RTI) at alewis@rti.org.

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1. Title

2. Authors and Affiliations (including lead author and co-investigators)

Author	Affiliation

3. Background and Rationale

4. Aims and Objectives

5. Short statement of significance of proposed research:

6. Nature of Research ☐ Validation ☐ Exploratory ☐ Other

7. Characteristics of patient population for analysis:

Diagnosis

- ☐ Marfan Syndrome
- ☐ Turner Syndrome
- ☐ Ehlers-Danlos Syndrome, vascular type
- ☐ Ehlers-Danlos Syndrome, other type and with aortic enlargement
- ☐ Loeys-Dietz Syndrome
- ☐ FBN1, TGFBR1, TGFBR2, ACTA2, or MYH11 genetic mutation
- ☐ BAV
- ☐ Familial Thoracic Aortic Aneurysm and Dissections with aortic enlargement
- ☐ Other aneurysms/dissections of the thoracic aorta in persons <50 years of age
- ☐ Other congenital heart disease with aortic enlargement

Age

☐ <5 ☐ 5-17

☐ 18-39 ☐ 40-69 ☐ >69

Gender

☐ Male ☐ Female

8. Describe GenTAC data requested for analysis:

- ☐ Surgical Data
- ☐ Pregnancies
- ☐ Quality of Life
- ☐ Organ system review
- ☐ Medication use
- ☐ Imaging Data
- ☐ Genetic Data
- ☐ Family History
- ☐ Demographics
- ☐ Other, specify below:

9. Other inclusion or exclusion criteria:

10. Describe GenTAC specimens requested for analysis:

☐ No specimens requested

Specimen Type	Amount per subject	Units
☐ Plasma		ml
☐ DNA		ug
☐ Viable cells		$x10^6$
☐ Tissue		☐ Snap frozen ☐ Blocks

11. Describe how GenTAC resources will be combined and used with existing data or samples (or type N/A):

12. Describe analysis plan including sample size and power calculation, type of analyses to be conducted, and draft of tables/graphs when applicable:

13. Who will conduct the analyses? ☐ Applicant ☐ RTI

14. Description of facilities at which the research will be conducted:

15. Estimated start and completion date:

16. Anticipated deadlines (e.g., abstract due dates):

17. Target journals, publications or conferences:

18. Source of funding for this proposal:

19. Status of IRB Approval ☐ Attached ☐ Pending ☐ N/A

NOTE 1

All genetic data (i.e., DNA sequencing, targeted genotyping, SNP analysis from GWAS studies, CNV, DNA methylation status, chromosome analyses/karyotyping, microarray) generated from GenTAC samples must be submitted to RTI International for deposition in the GenTAC genetic database within one year of the date of completion of the genetic analyses. At this time, the genetic data will become available to the research community. If additional time is required to protect the data prior to publication the investigators should contact RTI/GenTAC and request additional data embargo time. Investigators have exclusive rights to publish the analysis of their genetic data before it becomes available to others. The investigator will be contacted before genetic data is released to other investigators if GenTAC has not been informed that the study is completed. If investigators determine that the data will address a new research question not part of the approved proposal, they will inform GenTAC through submission of a new research proposal thereby requesting permission for expanded use of the data. Investigators using NIH funds to generate the genetic data are required to follow all NIH policies regarding access to genetic data. Use of the GenTAC resource constitutes use of NIH funds as it is a NIH sponsored registry.

NOTE 2

Publications of research that use GenTAC data or specimens must cite GenTAC using the following acknowledgement:

The GenTAC Registry has been supported by US Federal Government contracts HHSN268200648199C and HHSN268201000048C from the National Heart Lung and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Bethesda, MD).

To Be Completed by Data Coordinating Center:

Proposal Category:
- ☐ Ia (existing data only)
- ☐ Ib (existing data and specimens)
- ☐ II (additional data collection and funded by GenTAC)
- ☐ III (additional data collection and funded by outside source)

Additional IRB Required? ☐ Yes ☐ No

Tracking Number

Date 1st Received

Date Reviewed and Approved by OC*

Date Sent to SAB for Review

Date Revisions Needed Sent to Applicant ☐ N/A

Date Revised Received

Status of Original ☐ Approved ☐ Needs Revision ☐ Not Approved

Status of Revised ☐ Approved ☐ Not Approved

Date of Final Decision by OC

Date Final Decisions Sent to Requestor

Comments:

*** Preliminary OC approval indicates:**

- The proposed study does not interfere with other parts of the GenTAC protocol.
- The proposed study population and requested samples are available
- The proposal does not have significant overlap with proposed or on-going studies by GenTAC investigators,
- The proposed study will not significantly deplete GenTAC biospecimens
- The study will not hamper continued participation of study subjects in the registry.
- The study does not place an undue burden on the DCC and the GCCs.
- The timeline for completion is reasonable
- There are available funds to support the proposed study.