

Award Number: W81XWH-04-1-0896

TITLE: Tuberous Sclerosis Complex National Database

PRINCIPAL INVESTIGATOR: Steven P. Sparagana, M.D.

CONTRACTING ORGANIZATION: The University of Texas Southwestern Medical Center
Dallas, TX 75390

REPORT DATE: October 2006

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE 01-10-2006		2. REPORT TYPE Final		3. DATES COVERED 22 Sep 2005 – 21 Sep 2006		
4. TITLE AND SUBTITLE Tuberous Sclerosis Complex National Database				5a. CONTRACT NUMBER		
				5b. GRANT NUMBER W81XWH-04-1-0896		
				5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Steven P. Sparagana, M.D.				5d. PROJECT NUMBER		
				5e. TASK NUMBER		
				5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas Southwestern Medical Center Dallas, TX 75390				8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)		
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited						
13. SUPPLEMENTARY NOTES Original contains colored plates: ALL DTIC reproductions will be in black and white.						
14. ABSTRACT A Consortium was formed in July 2002 by the Tuberous Sclerosis Alliance (TSA) and tuberous sclerosis (TS) clinic personnel nationwide to begin discussions of natural history studies and development of a comprehensive clinical database (DB) to be used for both research and clinical purposes. The Consortium proposed to characterize the natural history of tuberous sclerosis complex (TSC) through development of an internet-based DB to collect comprehensive data on individuals with TSC. In July of 2005, TSA assumed control of the development process and contracted with a computer software designer, Tesuji, Inc. to begin development of the DB. Working Groups, a Steering Committee, and an Advisory Panel worked diligently to develop data collection points that were used by Tesuji, Inc. in the development phase. Development of the DB is complete and a pilot phase will begin in Fall 2006.						
15. SUBJECT TERMS Tuberous Sclerosis Complex, Database, Natural History						
16. SECURITY CLASSIFICATION OF:				UU	18. NUMBER OF PAGES 191	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	19b. TELEPHONE NUMBER (include area code)			

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Introduction

Our work involves the creation of an internet-based database (DB) to collect comprehensive data on individuals with tuberous sclerosis complex (TSC) in order to better define the natural history of TSC and to enable clinical research in TSC. This DB has been developed through the collaborative efforts of clinicians and scientists from all major TSC clinics in the United States and the Tuberous Sclerosis Alliance (TSA). The scope of this award allowed us to establish the administrative framework for the development of the DB and to bring development to its final stages. DB development is complete and is now being overseen by the TSA. Once the DB is fully online, subjects will be recruited on a voluntary basis from multiple tuberous sclerosis clinics throughout the United States, possibly from select international sites, as well as the TSA. A trial of the DB is scheduled to begin in Fall 2006 at two pilot sites. Data is to be collected both retrospectively and prospectively, with intent to capture data longitudinally.

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Body

The Tuberous Sclerosis Complex Clinical Database Consortium (TSCCDC or Consortium) was formed in July 2002 to begin discussions of a natural history study approach to understanding Tuberous Sclerosis Complex (TSC) and to develop a comprehensive clinical database (DB) that could be used for research purposes. The TSCCDC is composed of members of the major TSC clinics in the United States (US), one TSC clinic in the United Kingdom (UK), and the Tuberous Sclerosis Alliance (TSA).

A significant objective of the TSCCDC was to define the natural history and variability of TSC over the lifespan of individuals with the disease. Improved characterization of all clinical aspects of TSC will allow for more accurate prognosis of disease course, assist in the identification and development of targeted treatments, and will enhance our ability to gauge response to treatments as they are developed. Information from this study will also provide important insights about biological mechanisms of epilepsy, cognitive development, behavioral disorders, and cancer as these problems relate to individuals with TSC, as well as to the general population.

A mechanism by which the above-mentioned objective will be achieved is through the development of an internet-based DB used to collect comprehensive clinical information on individuals with TSC. The DB has been developed through the collaborative efforts of clinicians and scientists who make up the TSCCDC.

Through natural history studies and the establishment of the DB, the TSCCDC will provide for the acquisition, storage, and utilization of clinical data on approximately 2,000 individuals with TSC. This information will allow for a better description of the clinical course of individuals throughout the life cycle. The DB will also serve as an important research tool in launching investigations on specific clinical problems and TSC treatments. While several institutions have developed DBs to manage their TSC clinical data, there are no DBs of the breadth, magnitude and power as the one we have proposed. The TSCCDC chose to initiate development of the DB at The Scottish Rite Hospital for Children (TSRHC) because of prior experience in the development of a similar DB for another complex neurological disorder, holoprosencephaly (HPE).

As required by regulations set forth by the Department of Defense (DOD) Congressionally Directed Medical Research Programs (CDMRP) prior to formal application of our grant proposal, several tasks were outlined. One such task was the creation of a Statement of Work (SOW).

The SOW was submitted in May 2004 to the CDMRP as directed by the grant submission requirements. Once the grant was approved, work began in earnest on the accomplishment of the tasks delineated within the SOW. The original SOW has been provided in **Appendix B**.

One of the first tasks was to establish an administrative structure to guide development of the DB. Three key areas either identified by the TSCCDC or required by the DOD as part of this

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structure include a Steering Committee (SC), an Advisory Panel (AP), and Working Groups (WG).

WGs were originally established in November 2003 by the TSCCDC. These groups were comprised of professionals in the healthcare field and were created to reflect the key areas of interest in the treatment and research of subjects with TSC. These areas include epilepsy, cardiology, renal/urology, pulmonology, dermatology, cognition and behavior, genetics, and other organ involvement. The WG members were given the task of 1) identifying research questions regarding the natural history and progression of TSC and 2) identifying key fields to be included in the data collection tools. Since their inception, the WGs have met via teleconferencing on several occasions and in person in April 2004 and November 2004. A complete list of WG members is included in **Appendix C**.

In April 2004, a meeting was held at TSRHC in Dallas, Texas (TX), to further the progress of the DOD Natural History Development Award proposal. Those in attendance established an SC and an Executive Steering Committee (ESC) as required by DOD regulations. Members include both clinicians and consumers. Names and affiliations for both the SC and ESC have been provided in **Appendix D**. The function of the SC was to direct the development of the DB and data collection tools. The ESC was created in order to make decisions that needed to be made quickly and to approve the direction of project development.

Planning for the establishment of an AP, as set forth in the guidelines for the Natural History Planning Award, was begun at this meeting as well. Key advisory disciplines were identified and potential member names were suggested by the newly formed SC. Other members of the TSCCDC not on the SC were asked to submit possible AP members. A complete list of AP members is included in **Appendix E**. The AP included both clinicians and consumers as required by the DOD. The potential members were contacted over the course of the next few months with most members in place by early Fall 2004. The final members were secured in January 2005. The AP was in place to serve as a sounding board for the WG and SC members as they worked on field development and data collection tools. The AP members agreed to be available for one-two meetings per year but were primarily available by phone or email.

An application was made to the DOD by Dr. Steven P. Sparagana on behalf of the TSCCDC for a Natural History Planning Award in May 2004. The planning grant was officially awarded in September 2004. Work continued on the creation of the proposed DB in the meantime.

A meeting was held in November 2004, at TSRHC, to continue work on establishing data fields for a TSC DB. Members of the SC, some members of the WGs, and Information Technology (IT) from TSRHC met to discuss key data points that would be collected in the DB. Several areas were discussed in detail and initial fields were established. It was decided that a data collection tool would be created and circulated to several of the participating sites for a trial use period.

At the November 2004 meeting, it was decided that Dr. John Bissler from Cincinnati Children's Hospital Medical Center would submit a Natural History Study grant proposal to the DOD on the

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renal aspects of TSC on behalf of the TSCCDC. The proposal entitled Tuberous Sclerosis Complex Natural History Study: Renal Manifestations, was submitted in the Spring 2005.

Upon completion of the November 2004 meeting, the proposed fields were circulated to the WG and SC members for review. Based upon the results of the November meeting and feedback from the SC members, work was begun on an initial data collection tool.

Over the course of the next few months, drafts of specific sections of the tool were circulated to corresponding WG members as each section was completed. Once input was received from the WG members, revisions were considered and made if deemed appropriate. The tool was to be distributed to the entire WG membership upon completion. The WG members were available for consultation and were given the opportunity to review the data collection tools. Their work resulted in the development of drafts of an Initial Data Collection Tool and a Mortality Report Tool. These drafts are provided in **Appendices F and G**.

As part of the initial proposal process, specific aims of a future Natural History Study were developed and were included in the original grant proposal. During the meeting in November 2004, these specific aims were expanded upon. Several potential research questions/hypotheses were identified as well. Specific aims and representative research questions have been provided in **Appendix H**.

On April 9, 2005, Drs. Steven Sparagana and E. Steve Roach presented a brief review entitled Clinical Features and Natural History of TSC at the TSC/LAM (Lymphangiomyomatosis) International Research Symposium in Cincinnati, Ohio (OH). This review included a project update on the status of DB development. A copy of the abstract has been included as **Appendix I**.

Several administrative changes occurred at TSA during the course of the award cycle, some of which have directly affected the direction of DB development. The most notable change is that Nancy Taylor was hired as the new president of TSA in September 2004. Ms. Taylor has enthusiastically embraced the DB and Natural History study and has been instrumental in expediting transfer of the DB to the TSA ahead of schedule.

In July 2005, representatives from TSA, TSRHC and Tesuji, Inc., a software development company, met in Dallas, TX, to discuss ongoing development of the DB. It was decided that TSA would assume responsibility to develop and maintain the DB from that time forward. Nancy Taylor communicated this to the members of the TSCCDC, SC, AP and WGs in a letter dated September 21, 2005. This letter has been attached as **Appendix J**. The Tesuji, Inc., development plan for the DB has been attached as **Appendix K**.

Other administrative changes of note include contracting with Tesuji, Inc., of Denver, Colorado, (CO), to develop the software for the DB in July 2005. Michael Cinkosky is the president of Tesuji, Inc., and has been instrumental in the DB development. TSA also hired Jo Anne Nakagawa to facilitate the project internally within the TSA. Curricula Vitae (CVs) for both Ms.

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Nakagawa and Mr. Cinkosky were attached as appendices in the 2005 Annual Report submitted to the DOD.

Tesuji, Inc. began developing high-level goals and project scope in Summer 2005. The project analysis was completed in December 2005 and included domain analysis and workflow analysis. A DB design meeting was held in Chicago, Illinois (IL), in December 2005 to discuss the progress and future direction of the DB. Members of TSA, Tesuji, Inc., and TS clinic directors from around the country were in attendance.

Tesuji, Inc. was able to then move forward with the design phase. The design phase involved the creation of the user interface and the technical aspects of the DB and was completed in June 2006. The user interface is provided as **Appendix L**.

As a result of the administrative changes, TSA revised the SOW in July 2006 to reflect the work being performed under their guidance. It was submitted to Shannyn Scassero at the US Army Medical Research Acquisition Activity (USAMRAA) for approval in August 2006. At the writing of this report, we have not received a final approval for the revisions. The revised SOW has been provided in **Appendix M**.

The TSA Board of Directors appointed Vicky Whittemore, PhD, Elizabeth Thiele, MD, PhD, and Hope Northrup, MD, to form a new Steering Committee after the transition from TSRHC to TSA was complete. The members are listed in **Appendix N**. The SC members held monthly conference calls to review progress and deal with issues regarding construction of the DB.

TSA submitted the DB for review to a central IRB (Institutional Review Board), Independent Review Consulting, Inc., in March 2006. Approval was received in June 2006. A copy of the central IRB approval letter is provided as **Appendix O**. TSA also applied for a Certificate of Confidentiality (CoC) to the National Institutes for Health on behalf of all potential participating sites in June 2006. The CoC was received in August 2006. A copy of the CoC approval letter is provided as **Appendix P**.

Proposals for DB pilot site selection were solicited by TSA in May 2006. TSRHC and The Minnesota Epilepsy Group were selected as the two pilot sites after a review process. Each pilot site will apply to their local IRB for project approval before the trial begins. A copy of TSRHC's pilot site proposal is provided as **Appendix Q**. A draft copy of the pilot site contract is provided in **Appendix R**.

At the national TS conference held in July 2006 in Bloomingdale, IL, a meeting of TSC Clinic directors, clinical staff and research staff was held. The DB was unveiled to the attendees and a live demonstration was conducted. User manuals were also distributed.

Simultaneously with DB development, TSA has revised a Consortium Agreement which is provided in draft form in **Appendix S**. It will be finalized and presented to all TSC Clinic directors in Fall 2006 or Spring 2007.

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Patient recruitment tools including brochures and magazine articles in TS Perspectives are being developed and reviewed as of this writing. All materials must be approved by the IRB at each participating site before use. A draft copy of a recruitment brochure is provided in **Appendix T**.

Data collection tools have been developed using the early data collection tools drafted by TSRHC (**App. F**) as well as the design work conducted by Tesuji, Inc. These tools were finalized in Summer 2006 and may be used in paper or electronic form. Deployment of the DB on appropriate servers has been completed. Training at the two pilot sites was conducted in September 2006 by staff of TSA and Tesuji, Inc. A training schedule is provided in **Appendix U**.

The 6-month pilot phase is slated to begin when each of the trial sites receives IRB approval and subsequently submits that to TSA. TSA will monitor progress at each site one month after initiation by telephone. A site visit will be conducted by TSA midway through the pilot phase to ensure regulatory compliance and reliability of data entry. Technical support will be available from TSA.

As a result of the shift in DB development site and in the above-mentioned changes in management, there have been modifications to the administrative structure outlined previously. However, the specific aim and overall goals of the project remain unchanged. The development of a comprehensive DB has been achieved ahead of schedule.

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Key Research Accomplishments

- Solidified the relationship of the TSC clinicians and researchers who form the Tuberous Sclerosis Complex Clinical Database Consortium (TSCCDC). This group has worked together to ensure the development of a multicenter TSC DB.
- Established the administrative structure from the members of the TSCCDC. This administrative structure will oversee the continued development of the DB and aid in the identification of Natural History Studies that will ultimately utilize this DB.
- Formulated specific aims and hypotheses which may be further addressed in future Natural History Studies.
- Development of data collection tools including an Initial Data Collection Tool and a Mortality Report Tool which were used in the development of the DB by Tesuji, Inc.
- Based on the initial progress of the DB and success of the TSCCDC collaboration, Dr. John Bissler from Cincinnati Children's Hospital Medical Center submitted a Natural History Study grant proposal on the renal aspects of TSC on behalf of the TSCCDC. The proposal entitled Tuberous Sclerosis Complex Natural History Study: Renal Manifestations was submitted in the Spring 2005 and awarded to Dr. Bissler in September 2005.
- DB development completed Summer 2006.
- Pilot phase of DB to begin Fall 2006.

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Reportable Outcomes

- **Data Collection Tools**

The work on the project for this Natural History Development Award generated important data collection tools which were used to help guide the computer software developer in creating a usable, complete DB.

- **Funding for Natural History Study Award**

Based on the initial progress of the DB, Dr. John Bissler from Cincinnati Children's Hospital Medical Center submitted a Natural History Study grant proposal on the renal aspects of TSC on behalf of the Tuberous Sclerosis Complex Clinical Database Consortium (TSCCDC). The proposal entitled Tuberous Sclerosis Complex Natural History Study: Renal Manifestations was submitted in the Spring 2005. The grant was awarded to Dr. Bissler in September 2005.

- **Development of Database**

The focus of this project was to develop a DB that would be used by TSC clinicians and researchers in future Natural History Studies. Development has been completed ahead of schedule by Tesuji, Inc., using the data collection tools generated by the TSCCDC.

A 6-month pilot phase is scheduled to begin in Fall 2006 at Texas Scottish Rite Hospital for Children and another clinical site.

- **Presentations and publications**

On April 9, 2005, Drs. Steven Sparagana and E. Steve Roach presented a brief review entitled Clinical Features and Natural History of TSC at the TSC/LAM (Lymphangiomyomatosis) International Research Symposium in Cincinnati, Ohio (OH). This review included a project update on the status of DB development. A copy of the abstract has been included as **Appendix I**.

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Conclusion

For many years, key Tuberous Sclerosis Complex (TSC) clinicians and researchers have expressed the desire for a multicenter TSC Database (DB) that would allow for the collection of comprehensive data on individuals with TSC. The Tuberous Sclerosis Complex Clinical Database Consortium was formed with the intent to create such a DB.

This Natural History Planning Award has fostered a renewed desire to achieve the goal of a multicenter DB. It allowed the TSCCDC to develop into a more cohesive group whose goal was the creation of a DB that will facilitate Natural History Studies leading to a better understanding of TSC and to facilitate clinical research on TSC.

The Tuberous Sclerosis Alliance (TSA) has played a significant role in the development of the DB by hiring a DB manager to oversee the development effort, and by contracting with a software developer to help create the DB.

These collaborative efforts to develop a comprehensive, multicenter DB on individuals with TSC have been extraordinarily fruitful. The DB has been created, and a pilot phase will soon commence at two of the TSC clinics. Release of the DB to other TSC clinics is envisioned in mid 2007. Once enough data has been acquired, we will have the opportunity to improve understanding of the natural history of TSC, and we can begin to address the many important questions about the disorder. Work on this project has been completed on or ahead of schedule. Overall, this endeavor has been a great success for the TSC clinical community and the TSA. Patients and families affected by TSC will experience the ultimate benefit.

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References

There were no relevant references used in the preparation of this annual report.

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Appendix A – Abbreviations

AP	Advisory Panel
CDMRP	Congressionally Directed Medical Research Programs
CO	Colorado
CoC	Certificate of Confidentiality
CV	Curriculum Vitae; Curricula Vitae
DB	Database
DOD	Department of Defense
ESC	Executive Steering Committee
HPE	Holoprosencephaly
IL	Illinois
IRB	Institutional Review Board
IT	Information Technology
LAM	Lymphangiomyomatosis
OH	Ohio
SC	Steering Committee
SOW	Statement of Work
TSA	Tuberous Sclerosis Alliance
TSC	Tuberous Sclerosis Complex
TSCCDC	Tuberous Sclerosis Complex Clinical Database Consortium
TSRHC	Texas Scottish Rite Hospital for Children
TX	Texas
US	United States
USAMRAA	United States Army Medical Research Acquisition Activity
UK	United Kingdom
WG	Working Group(s)

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Appendix B – Statement of Work (Original)

Task 1: Set up administrative structure to oversee development of the database (DB)

- Working groups (WG) established November 2003. Several groups have been meeting regularly via teleconferences and will continue to do so.
 - Task was to develop fields to be included in DB by establishing key scientific questions. Focus areas include: Epilepsy/EEG, Brain Lesions/MRI/other CNS Imaging, Dermatology, Renal, Neuropsychological/Behavioral/Cognition, Pulmonary, Genetics/Family History, Other Organ Systems and Registry (WG pending).
 - A list of WG members will be provided upon request.
- Planning meeting held on April 13, 2004.
- Steering Committee (SC) formally established April 13, 2004.
 - Members are listed in Proposal Body.
- Formation of Advisory Panel. April-August 2004.
 - Names were submitted for review by members of the SC. Contact will be made and members secured by end of August 2004.
- Identification of Phase I and Phase II sites. April-May 2004.
 - Phase I sites will be the primary sites involved in development and testing of the DB and for subject enrollment; Phase II sites will be added once the DB is up and running smoothly.
 - Sites are listed in Proposal Body.

Task 2: Drafting and approval of Consortium Agreement

- Consortium Agreement drafted January 2004.
 - Draft copy is included with the Proposal under the Administrative Documentation section.
- Final draft to be circulated between SC, Phase I and Phase II site members. July 2004.
- Approval and signatures to be obtained by the end of July 2004.

Task 3: Development of data fields for DB

- Fields for DB to be developed by WGs. January-December 2004.
- WG will also define how to standardize data between clinical sites, e.g., volumetric measurement of cortical tubers on MRI. January-December 2004.
- Teleconferences will be held throughout 2004 to accomplish this task.

Task 4: Meeting of key WG members with Texas Scottish Rite Hospital for Children (TSRHC) Information Technology (IT) staff

- Key WG members, SC members, Advisory Panel and IT staff to finalize data fields. October-November 2004.
- Revised data fields to be circulated to all WG members for final approval. November-December 2004.
- Data fields presented to IT staff to commence DB construction. December 2004.

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Task 5: Creation of the DB

- Identification of a third-party vendor for programming needs. November-December 2004.
- Initial programming of fields. January-September 2005.

Task 6: Initial DB prototype review and revision

- Meeting with key WG members, SC, and IT staff to review initial prototype. Spring 2005.
- Revision of DB. September-December 2005.

Task 7: Institutional Review Board approval

- Will seek overall project approval August 2004.
- Consent forms to be written and submitted for approval. December 2005-April 2006.

Task 8: Define patient selection process

- Identification of sample size and description of patient population at each site. July-August 2004.
- Identify methods to minimize selection bias (e.g., to ensure that mildly affected individuals are proportionally represented in DB). July-August 2004.

Task 9: DOD TSC Natural History Study grant proposal

- Prepare and submit DOD TSC Natural History Study grant proposal March-May 2005.

Task 10: Formation of a patient-initiated registry

- Registry to be developed as a separate component of the DB to collect contact and demographic information from potential subjects for future TSC research projects. June-August 2005.

Task 11: Development of data collection tools

- Develop data collection forms. December 2005-June 2006.
- Meeting with key WG members and SC members to finalize data collection tools. Spring 2006.
- Develop training protocol. December 2005-June 2006.

Task 12: Site visit for training

- Site visits to Phase I clinics for training of data collection personnel January-March 2006.
 - This task may be accomplished by data collection personnel visiting TSRHC for training.

Task 13: Application for Certificate of Confidentiality

- Application will be made to the Department of Health and Human Services for the DB project as a whole. May 2006.

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Task 14: Development of information dissemination web site

- Develop a web site that provides information about the TSC National DB and gives some statistics about enrollment, projects to date, planned projects, recruitment information and a link to the TSC patient-initiated registry. July-August 2006.

Task 15: Piloting test DB

- Troubleshooting data input/output. January 2006.
- Revision of DB. February 2006.
- Subsequent DB trial. March 2006.

Task 16: Development of patient recruitment tools

- Patient recruitment tools to be developed by key Steering Committee and Phase I site members. January 2006-July2006.
 - Tools to include brochures, videos, and other materials as yet to be determined.
- All tools will be submitted for IRB approval prior to use.

Task 17: Database go-live

- Subject recruitment and data entry to begin. July 2006.

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Appendix C – Working Groups

1. CNS

1A - Epilepsy/EEG

Elizabeth Thiele, MD, PhD (Boston) –
Chair
Director, Pediatric Epilepsy Program
Massachusetts General Hospital
VBK 830
55 Fruit Street
Boston, MA 02114
617-726-6540
ethiele@partners.org

Lori Batchelor, RN, MHSM (Dallas)
Texas Scottish Rite Hospital for Children
Neurology Department
2222 Welborn St.
Dallas, TX 75219
214-559-7824
lori.batchelor@tsrh.org

Peter Crino, MD, PhD (Philadelphia)
University of Pennsylvania Medical
Center
Department of Neurology
3400 Spruce Street
Philadelphia, PA 19104
215-249-5312
crinop@mail.med.upenn.edu

Kevin Ess, MD, PhD (St. Louis)
Fellow, Pediatric Epilepsy Center
St. Louis Children's Hospital
Division of Pediatric Neurology
One Childrens Place
St. Louis, MO 63110
314-454-4089
essk@neuro.wustl.edu

David Franz, MD (Cincinnati)
Cincinnati Childrens Hosp. Med. Ctr.
3333 Burnet Ave.
Cincinnati, OH 45229
513-636-4222
david.franz@chmcc.org

Mike Frost, MD (Minnesota)
Minnesota Epilepsy Group, P.A.
310 Smith Avenue North, Ste. 300
St. Paul, MN 55102
651-241-5290
mfrost@mnepilepsy.net

Dan Miles, MD (New York)
New York University School of Medicine
Division: Neurology
Department: Epilepsy Center
550 First Avenue
New York, NY 10016-6481
Tel: (212) 263-8318
milesd01@popmail.med.nyu.edu

Steve Roach, MD (Winston-Salem)
Director, Comprehensive Epilepsy Center
Wake Forest University
Department of Neurology
1 Medical Center Drive
Winston-Salem, NC 27157
336-716-4101
sroach@wfubmc.edu

Steven Sparagana, MD (Dallas)
Director, TS Clinic
Texas Scottish Rite Hospital for Children
Neurology Department
2222 Welborn St.
Dallas, TX 75219
214-559-7828
steven.sparagana@tsrh.org

Catherine Thompson, BS (Dallas)
Texas Scottish Rite Hospital for Children
Neurology Department
2222 Welborn St.
Dallas, TX 75219
214-559-7818
catherine.thompson@tsrh.org

Vicky Whittemore, PhD (Silver Spring)
Sr. Science Advisor
Co-dir., Center Without Walls
Tuberous Sclerosis Alliance
801 Roeder Road, Ste. 750
Silver Spring, MD 20910
800-225-6872
vwhittemore1@comcast.net

1B - Lesions/MRI/other CNS imaging

Lori Batchelor, RN, MHSM (Dallas)
See section 1A

Peter Crino, MD, PhD (Philadelphia)
See section 1A

David Franz, MD (Cincinnati)
See section 1A

Mike Frost, MD (Minnesota)
See section 1A

Bill McClintock, MD (Washington, DC)
Children's National Medical Center
Ass. Prof. of Neurology and Pediatrics
The Geo. Washington Univ. Med. Ctr.
111 Michigan Ave., NW
Washington, DC 20010-2970
202-884-5000
wmclint@cnmc.org

Steve Roach, MD (Winston-Salem)
See section 1A

Steven Sparagana, MD (Dallas)
See section 1A

Catherine Thompson, BS (Dallas)
See section 1A

Vicky Whittemore, PhD (Silver Spring)
See section 1A

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2. Neuropsychological, behavioral and psychiatric/ Developmental milestones

Lori Batchelor, RN, MHSM (Dallas)

See section 1A

Ann Byars, PhD (Cincinnati)

Department of Neurology
Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, OH 45229-3039
651-241-5288
anna.byars@cchmc.org

Petrus de Vries, MD, PhD (Cambridge, UK)

University of Cambridge
Department of Psychology
Developmental Psychology Section
Douglas House
18b Trumpington Road
Cambridge CB2 2AH
+44(0) 1223 746050
pd215@cam.ac.uk

Ann Hempel, PhD (Minnesota)

Minnesota Epilepsy Group, P.A.
310 Smith Avenue North, Ste. 300
St. Paul, MN 55102
651-241-5290
ahempel@mnepilepsy.net

Bryan King, M.D. (Dartmouth)

Dartmouth University
Department of Psychiatry
Dartmouth-Hitchcock Medical Center,
Children's Hosp. at Dartmouth (CHaD)
HB 7750
Lebanon, NH 03756
603-650-5835
Bryan.H.King@dartmouth.edu

Penny Prather, Ph.D. (Boston)

Educational Enhancement Center
23 Pleasant Street
Newton, MA 02459
617-332-4141
pprather@rcn.com

Catherine Thompson, BS (Dallas)

See section 1A

Vicky Whittemore, PhD (Silver Spring)

See section 1A

Charles Zaroff, PhD (NYU)

Comprehensive Epilepsy Center
Phone: (212) 263-8317
Fax: (212) 263-8342
charles.zaroff@med.nyu.edu

3. Dermatology

Lori Batchelor, RN, MHSM (Dallas)

See section 1A

Thomas Darling, MD (Bethesda)

Uniformed Services
University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814
800-515-5257
tdarling@mxc.usuhs.mil

Cheryl Dunigan, PhD (Silver Spring)

Vice Pres., Scientific Affairs
Tuberous Sclerosis Alliance
801 Roeder Road, Ste. 750
Silver Spring, MD 20910
800-225-6872
cheryl.dunigan@tsalliance.org

Mark Mausner, MD (Washington, DC)

11119 Rockville Pike, Suite 501
Rockville, MD 20852
301-984-8804
tucknlift@aol.com

Elizabeth McBurney, MD (New Orleans)

Medical Office Building
1051 Gause Blvd., Ste. 460
Slidell, LA 70459
504-649-5369
skincarepecial@aol.com

Keyomaurs Soltani, MD (Chicago)

University of Chicago
Department of Medicine
Section of Dermatology
5841 S. Maryland Avenue, MC 5067
Chicago, IL 60637
773-702-6559
ksoltani@medicine.bsd.uchicago.edu

Catherine Thompson, BS (Dallas)

See section 1A

Vicky Whittemore, PhD (Silver Spring)

See section 1A

4. Renal/Liver/GI

Lori Batchelor, RN, MHSM (Dallas)

See section 1A

John Bissler, MD (Cincinnati)

Ass. Prof. of Pediatrics
Children's Hosp. Research Found.
Div. of Nephrology and Hypertension
3333 Burnet Ave., ML#7022
Cincinnati, OH 45229-3039
513-636-4531
bissj0@chmcc.org

David Ewalt, MD (Dallas)

Urology Clinics of North Texas
8315 Walnut Hill Lane, Ste. 205
Dallas, TX 75231
214-750-0808
dhewalt@pol.net

John Hulbert, MD (Minnesota)

Urology Physicians
6363 France Ave. S #500
Edina, MN 55439
952-920-7660
jhulb3317@aol.com

Chris Kingswood, MD (UK)

19 Sadler's Way
BN8 5HG Ringmer, East Sussex
U.K.
0 (127) 369-6955
chris.kingswood@bsuh.nhs.uk

Catherine Thompson, BS (Dallas)

See section 1A

Vicky Whittemore, PhD (Silver Spring)

See section 1A

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5. Pulmonary

Lori Batchelor, RN, MHSM (Dallas)
See section 1A

Frank McCormack, MD (Cincinnati)
University of Cincinnati
Pulmonary Division
231 Albert Sabin Way MSB 6007
Cincinnati, OH 45267
513-558-0480
frank.mccormack@uc.edu

Catherine Thompson, BS (Dallas)
See section 1A

Vicky Whittemore, PhD (Silver Spring)
See section 1A

6. Cardiac

Lori Batchelor, RN, MHSM (Dallas)
See section 1A

Steve Roach, MD (Winston-Salem)
See section 1A

Vicky Whittemore, PhD (Silver Spring)
See section 1A

Fran DiMario, MD (CT)
282 Washington St., Ste. 2a
Hartford, CT 06106
860-545-9460
fdimario@ccmckids.org

Catherine Thompson, BS (Dallas)
See section 1A

7. Genetics

Lori Batchelor, RN, MHSM (Dallas)
See section 1A

Catherine Thompson, BS (Dallas)
See section 1A

****Aimee Williams, MS, CGC**
(Houston)

Hope Northrup, MD (Houston)
UT Houston Health Science Center
Div. of Medical Genetics
6431 Fannin St. MSB 3.1444
Houston, TX 77030
713-500-5761
hope.northrup@uth.tmc.edu

Vicky Whittemore, PhD (Silver Spring)
See section 1A

Assistant Professor
UT Medical School at Houston
Dept. of Pediatrics, Div. of Med. Genetics
6431 Fannin, MSB 3.147
Houston, TX 77030
713-500-5689
aimee.j.tucker@uth.tmc.edu

8. Other organ involvement

Lori Batchelor, RN, MHSM (Dallas)
See section 1A

Steven Sparagana, MD (Dallas)
See section 1A

Vicky Whittemore, PhD (Silver Spring)
See section 1A

Steve Roach, MD (Winston-Salem)
See section 1A

Catherine Thompson, BS (Dallas)
See section 1A

**Aimee Williams is no longer affiliated with UTH and lives outside of the US. She is no longer available for this Working Group.

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Appendix D – Executive Steering Committee and Steering Committee (Original)

Executive Steering Committee

Lori Batchelor, MHA, RN
Research Coordinator
Texas Scottish Rite Hospital for
Children
Neurology Department
2222 Welborn Street
Dallas, TX 75219

****Cheryl Dunigan, PhD**
Vice President, Scientific Affairs
Tuberous Sclerosis Alliance
801 Roeder Road Suite 750
Silver Spring, MD 20910

David Ewalt, MD
Urology Clinics of North Texas
8315 Walnut Hill Lane
Suite 205
Dallas, TX 75231

Wyatt Howell, MBA
Administrative Director, Neurology
Department
Texas Scottish Rite Hospital for
Children
Neurology Department
2222 Welborn Street
Dallas, TX 75219

Hope Northrup, MD
Director, Division of Medical Genetics
University of Texas Health Science
Center
Division of Medical Genetics
6431 Fannin St. MSB 3.1444
Houston, TX 77030

Steven Sparagana, MD
Director, TSC Clinic
Texas Scottish Rite Hospital for
Children
Neurology Department
2222 Welborn Street
Dallas, TX 75219

E. Steve Roach, MD
Director, Comprehensive Epilepsy
Clinic
Wake Forest University
Department of Neurology
1 Medical Center Drive
Winston-Salem, NC 27157

Catherine Thompson, BS
Research Coordinator
Texas Scottish Rite Hospital for
Children
Neurology Department
2222 Welborn Street
Dallas, TX 75219

Vicky Whittemore, PhD
Sr. Science Advisor
Tuberous Sclerosis Alliance
801 Roeder Road Suite 750
Silver Spring, MD 20910

Steering Committee

John Bissler, MD
Associate Professor of Pediatrics
Children's Hospital Research
Foundation
Division of Nephrology and
Hypertension
3333 Burnet Avenue ML #7022
Cincinnati, OH 45229

Peter Crino, MD, PhD
University of Pennsylvania Medical
Center
Department of Neurology
3400 Spruce Street
Philadelphia, PA 191104

Petrus deVries, PhD
University of Cambridge
Section of Developmental Psychiatry
Douglas House
18b Trumpington Road
Cambridge CB2 2AH

Fran DiMario, MD
282 Washington Street
Suite 2a
Hartford, CT 06106

Kevin Ess, MD, PhD
St. Louis Children's Hospital
Division of Pediatric Neurology
One Children's Place
St. Louis, MO 63110

David Franz, MD
Cincinnati Childrens Hospital Medical
Center
3333 Burnet Ave.
Cincinnati, OH 45229

Michael Frost, MD
Minnesota Epilepsy Group, P.A.
310 Smith Avenue North
Suite 300
St. Paul, MN 55102

John Hulbert, MD
Urology Physicians
6363 France Avenue S. #500
Edina, MN 55439

Josiane Lajoie, MD
NYU Comprehensive Epilepsy Center
403 East 34th Street
4th Floor
New York, NY 10016

Elizabeth Thiele, MD PhD
Director, Pediatric Epilepsy Program
Massachusetts General Hospital
VBK 830
55 Fruit Street
Boston, MA 02114

****Cheryl Dunigan is no longer working with the TSA and is not available for this committee.**

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Appendix E – Advisory Panel

Advisory Panel member names and area of expertise:

**Jack Arbiser, MD, PhD -
Dermatology**

Emory Clinic
Dermatology Department
Bldg. A., 1st Floor/Ste. A-1100
1365 Clifton, NE
Atlanta, GA 30332

**Mike Assell, PhD - Cognition and
Behavior**

University of Texas Health Science
Center Houston
PO Box 20036
Houston, TX 77225

Judy Bean, PhD - Statistics

CCHMC
3333 Burnet Ave.
MLC: 5041
Cincinnati, OH 45229

Gerald Beck, PhD - Epidemiology

Department of Biostatistics and
Epidemiology/Wb4
9500 Euclid Avenue
Cleveland, OH 44195

Richard Browne, PhD - Statistics

Texas Scottish Rite Hospital for
Children
Research Department
2222 Welborn Street
Dallas, TX 75219

**Jyoti Cameron - Consumer
(Adult with TSC)**

1008 Al Gregg Street
Houston, TX 77009

**Nancy Clegg, PhD, RN - Database
Construction**

Texas Scottish Rite Hospital for
Children
Neurology Department
2222 Welborn Street
Dallas, TX 75219

**Katrina Dipple, MD, PHD -
Genetics**

UCLA Human Genetics
5335B Gonda
Los Angeles, CA 90095

**Jan Friedman, MD, PhD -
Natural History Study**

Children's & Women's Health
Centre of BC
Medical Genetics Department
4500 Oak St., Rm. C234
Vancouver V6H 3N1

**Bonnie Gould Rothberg, MD -
Patient Registry**

The Rothberg Institute for
Childhood Diseases
530 Whitfield Street
Guilford, CT 06437

**Laura Jensen - Consumer (Parent
of child with TSC)**

7113 NE 168th Street
Bothell, WA 98011

**M. Regina Lantin-Hermoso, MD -
Cardiology**

University of Houston Health
Science Center
PO Box 20708
Houston, TX 77225-0708

Fray Marshall, MD - Renal

The Emory Clinic
1365 Clifton Road
Atlanta, GA 30322

**Dixon Moody, MD -
Radiology/Imaging**

Wake Forest University Medical
Center
Department of Radiology
Meads Hall, 2nd Floor
Medical Center Boulevard
Winston-Salem, NC 27157

Tony Riela, MD - Epilepsy

Texas Child Neurology, LLP
1708 Coit Road, Suite 150
Plano, TX 75075

Lisa Roach - Attorney

333 Fairfax Drive
Winston-Salem, NC 27104

Jay Ryu, MD - Pulmonary

Mayo Clinic
Pulmonary and Critical Care
Medicine
200 First Street S.W.
Rochester, MN 55905

**Arthur Sagalowsky, MD -
Oncology**

University of Texas Southwestern
Medical Center
5323 Harry Hines Boulevard
J8.114, MC 9110
Dallas, TX 75390-9110

Adil Shamoo, PhD - Ethicist

University of Maryland School of
Medicine
Department of Biochemistry and
Molecular Biology
108 N. Greene Street
Baltimore, MD 21201

**Howard Weiner, MD -
Neurosurgery**

New York University Medical
Center
Department of Pediatric
Neurosurgery
317 East 34th Street
Suite 10-02
New York, NY 10016

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Appendix F – Data Collection Tool

Tuberous Sclerosis Complex (TSC) Database
Data Collection Form -- Initial Visit
(Please print all information and check appropriate responses)

Today's Date (mm/dd/yyyy) ____ / ____ / ____

I. DEMOGRAPHICS

Subject's Full Name (first/middle/last): _____
Age: ____ Date of Birth (mm/dd/yyyy): ____ / ____ / ____ Birthplace (City/State/Country): _____ Sex: M F
Race (check all that apply): W-White H-Hispanic B-Black OA-Oriental Asian AI-American Indian PI-Pacific
Islander MEA-Middle Eastern Asian Other (list): _____
Highest school grade level attended: elementary junior high high school junior college college post graduate
Primary Language Spoken in the Household: _____ Occupation (If applicable): _____
Age TSC first diagnosed: ____ month(s) ____ year(s) Diagnosis classified as: Definite Probable Possible

Biological Mother's Name (first/middle/maiden/last): _____
Age: ____ Date of Birth (m/d/y): ____ / ____ / ____ Race (check all that apply): W H B OA AI PI
 MEA Other _____
Occupation: _____
Highest school grade level attended: elementary junior high high school junior college college post graduate
Street Address: _____ Apartment #: _____
City, State: _____ Zip Code: _____ Country: _____
Home Phone #: _____ Work #: _____ Alternate #: _____
Fax #: _____ E-mail Address: _____

Biological Father's Name (first/middle/last): _____
Age: ____ Date of Birth (m/d/y): ____ / ____ / ____ Race (check all that apply): W H B OA AI PI
 MEA Other _____
Occupation: _____
Highest school grade level attended: elementary junior high high school junior college college post graduate
Street Address: _____ Apartment #: _____
City, State: _____ Zip Code: _____ Country: _____
Home Phone #: _____ Work #: _____ Alternate #: _____
Fax #: _____ E-mail Address: _____

Name of Legal Guardian (first/middle/last): _____ Relationship to patient: _____
Street Address: _____ Apartment #: _____
City, State: _____ Zip Code: _____ Country: _____
Home Phone #: _____ Work #: _____ Alternate #: _____
Fax #: _____ E-mail Address: _____

For Center Use Only

Database ID:	TSC Consortium Site:	Medical Record #:
DB Consent: <input type="checkbox"/> Y <input type="checkbox"/> N	Form completed by: _____	Registry: <input type="checkbox"/> Y <input type="checkbox"/> N

Subject name: First, Middle, Last _____

DOB: _____

II. VITAL PHYSICAL DATA

Height _____ cm	Pulse _____
Weight _____ kg	Respirations _____
FOC _____ cm	BP _____

III. GENETICS

GENETIC TESTING

Was prenatal TSC genetic testing performed: Yes No Unknown

If yes, what was the result: TSC1 TSC2 Unknown

Was TSC genetic testing performed: Yes No Unknown

If yes: Athena or Research lab: Northrup Kwiatkowski Sampson Netherlands Other (list)

Was mutation identified: Yes No Unknown

If yes: TSC1 TSC2 Mutation (list) _____

Type of mutation (check all that apply):

Large gene deletions/rearrangements/insertions Yes No Unknown

Small mutation Yes No Unknown

If yes, check the mutation that applies: Protein truncation Small deletion/insertion Nonsense

Missense Unknown

Other variation (polymorphism) detected in TSC1 TSC2

If mutation was not found, are you enrolled in another genetic study: Yes No Unknown

If yes, check all that apply: Northrup Sampson Other (list) _____

Was blood or tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA)

Yes No Unknown

If yes, indicate location of bank and physician who banked sample: _____

FAMILY HISTORY OF TSC

Is subject the result of a multiple gestation: Yes No Unknown (e.g., adopted, foster child, etc.)

If subject is the product of a multiple birth, how many siblings: _____

Do any have TSC: Yes No Unknown

Are siblings: Fraternal Identical Mixed fraternal and identical

If subject is a twin, which type: Fraternal Identical

Does twin have TSC: Yes No Unknown

Are there other multiple births in family history: Yes No Unknown

Familial history of TSC: Yes No Unknown Adopted

If yes, how many generations are affected: 1 2 3 4 5 >5 Unknown

How many known affected family members: 1 2 3 4 >4 Unknown

If yes: Mosaic within one generation Mosaic parent/germline child(ren) – two generations Multigenerational

Have subject's parents had any of the following exams/evaluations:

Mother: Yes No Unknown

If yes, indicate which tests were performed:

TSC genetic testing

Brain imaging

Subject name: First, Middle, Last _____

DOB: _____

Renal imaging

Eye exam

If eye exam was performed, check all that apply: Ophthalmologist Optometrist Other MD

Skin exam

If skin exam was performed, check all that apply: Dermatologist Other MD

Father: Yes No Unknown

If yes, indicate which tests were performed:

TSC genetic testing

Brain imaging

Renal imaging

Eye exam

If eye exam was performed, check all that apply: Ophthalmologist Optometrist Other MD

Skin exam

If skin exam was performed, check all that apply: Dermatologist Other MD

ASSISTED REPRODUCTIVE TECHNOLOGY

Was subject conceived using Assisted Reproductive Technology (ART) Yes No Unknown

Egg donation Yes No Unknown

Sperm donation Yes No Unknown

In Vitro Fertilization (IVF) Yes No Unknown

IVF + Intracytoplasmic sperm injection (ICSI) Yes No Unknown

Preimplantation Genetic Diagnosis (PGD) Yes No Unknown

Singleton birth Yes No Unknown

Multiple birth Yes No Unknown

If multiple, how many: _____

IV. PRENATAL HISTORY

Was subject's diagnosis of TSC discovered during gestation: Yes No Unknown

If yes, by which method:

Chorionic villus sampling (CVS)/genetic testing

Amniocentesis/genetic testing

High-resolution echocardiography

Routine ultrasound

Fetal MRI

Other (list) _____

Were there any complications during subject's gestation: Yes No Unknown

If yes, indicate which complications occurred:

Maternal gestational diabetes

Maternal infection

Maternal seizures

Maternal substance abuse

Premature rupture of membranes

Premature birth

Other (list) _____

Were any of the following procedures performed during subject's gestation: Yes No Unknown

If yes, check all that apply:

Chorionic villus sampling (CVS)

Amniocentesis

Genetic testing

Routine ultrasound

Subject name: First, Middle, Last _____

DOB: _____

Fetal MRI

Other (list) _____

What was the estimated gestational age (EGA) at birth: _____ weeks

Was subject born by: Vaginal delivery Cesarean section Unknown

Were there any complications during or immediately after birth: Yes No Unknown

If yes, check all that apply:

Prolonged labor

Failure to progress

Decreased fetal heart rate

Meconium present

Low Apgar scores

1-minute score _____ Unknown

5-minute score _____ Unknown

Resuscitation:

Major Minor

Seizure

Other (list) _____

V. DERMATOLOGY

Has subject ever been evaluated by dermatologist for TSC finding: Yes No Unknown

If yes, for diagnostic purposes for treatment for both

Is subject currently followed by dermatologist: Yes No Unknown

SKIN

Hypomelanotic macules: Yes No Unknown

If yes: 1-3 4-6 ≥6

Size and location of largest three:

Size _____ cm; location _____

Size _____ cm; location _____

Size _____ cm; location _____

Diagnosed by: Visual inspection Woods lamp

Subject's age when hypomelanotic macules first noted: _____ month(s) _____ year(s)

Treatment: Yes No Unknown

If yes: Makeup Other (list) _____

Confetti lesions: Yes No Unknown

If yes: Right arm (RA) Right leg (RL) Left arm (LA) Left leg (LL) Other (list) _____

Subject's age when confetti lesions first noted: _____ month(s) _____ year(s)

Scalp fibroma: Yes No Unknown

Signs and symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Difficulty combing/brushing hair

Pain

Bleeding

Infection

Other (list) _____

Treatment: Yes No Unknown

Surgical excision

Other (list) _____

Subject's age when scalp fibroma first noted: _____ month(s) _____ year(s)

Subject name: First, Middle, Last _____

DOB: _____

Forehead fibroma: Yes No Unknown

Signs and symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Bleeding

Other (list) _____

Treatment: Yes No Unknown

Surgical excision

Other (list) _____

Subject's age when forehead fibroma first noted: _____ month(s) _____ year(s)

Angiofibroma: Yes No Unknown

If yes: <10 ≥10

Texture: Flat Raised

Location: Cheeks Chin Nose Nasolabial folds Forehead

Distribution: Unilateral Bilateral

Color (does not apply to black skin): Normal Pink Red Brown

Signs and symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Bleeding

Infection

Other (list) _____

Treatment: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

Treatment	Number of times treatment was performed
<input type="checkbox"/> Laser removal	_____
<input type="checkbox"/> Dermabrasion	_____
<input type="checkbox"/> Cryosurgery	_____
<input type="checkbox"/> Surgical excision	_____
<input type="checkbox"/> Other (list) _____	_____

Subject's age when angiofibroma first noted: _____ month(s) _____ year(s)

Shagreen patch: Yes No Unknown

If yes, location: Lumbosacral Region Other (list) _____

Treatment: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

Surgical excision

Other (list) _____

Subject's age when shagreen patch first noted: _____ month(s) _____ year(s)

Other: (choose all that apply)

Café au lait macule

Skin tags

Miliary fibroma (defined as slightly raised skin papules tinier than a pin head)

Other (list) _____

Biopsy:

Was a biopsy performed on any of the above mentioned skin findings: Yes No Unknown

If yes, indicate tissue/finding: _____

Results if known: _____

NAILS

Ungual fibroma: Yes No Unknown

If yes, location (indicate digit(s) - 1, 2, 3, 4, 5 with thumb and great toe being digit #1):

Right hand (RH) _____

Left hand (LH) _____

Subject name: First, Middle, Last _____

DOB: _____

Right foot (RF) _____

Left foot (LF) _____

Symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

_____ Indicate all digits affected (e.g., RH-1, LF-2)

Bleeding _____

Infection _____

Loss of nail _____

Other (list): _____

Treatment: Yes No Unknown

Surgical excision Number of times treatment performed _____

If excised, did any of excised tissue recur: Yes No Unknown

If yes, which tissue recurred: _____

Other (list) Number of times treatment performed _____

HAIR

Poliosis: Yes No Unknown

If yes, indicate location: Scalp hair Eyebrows Eyelashes Other (list) _____

VI. DENTAL

Has subject ever been evaluated by dentist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both

Is subject currently followed by dentist: Yes No Unknown

Pitting: Yes No Unknown

If yes, is/was pitting present in baby teeth: Yes No Unknown N/A

If yes, number of pits: 1-5 6-10 11-15 >15

Are any pits crater-like: Yes No Unknown

Is pitting present in permanent teeth: Yes No Unknown N/A

If yes, number of pits: 1-5 6-10 11-15 >15

Are any pits crater-like: Yes No Unknown

Symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Pain

Secondary decay

Other (list) _____

Treatment: Yes No Unknown

If yes, list treatment: _____

Gingival Fibroma: Yes No Unknown

If yes, number present: 1 2-4 >4

Symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Bleeding

Pain

Other (list) _____

Treatment: Yes No Unknown

If yes, indicate what treatment was performed:

Surgical excision Number of times treatment performed _____

If excised, did any of excised tissue recur: Yes No Unknown

Other (list) _____

Subject name: First, Middle, Last _____

DOB: _____

Gingival Hyperplasia: Yes No Unknown

If yes, has subject been prescribed phenytoin (PHT): Yes No Unknown

If PHT was prescribed, drug used in past drug currently used

Symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Bleeding

Other (list) _____

Treatment: Yes No Unknown

If yes, indicate what treatment was performed:

Surgical excision Number of times treatment performed _____

If excised, did any of excised tissue recur: Yes No Unknown

Other (list) _____

Cavities:

Does subject have a history of cavities: Yes No Unknown

VII. OPHTHALOMOLOGY

Has subject ever been evaluated by ophthalmologist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both

Is subject currently followed by ophthalmologist: Yes No Unknown

RETINAL FINDINGS

Retinal Findings: Yes No Unknown

If yes, complete this section. If No or Unknown, skip to the Non-Retinal Findings (this section).

Hamartoma: Yes No Unknown

--Mulberry lesion: Yes No Unknown

If yes, indicate location: Right Left Bilateral Unknown

Symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Visual loss

Pain

Hemorrhage

Other (list) _____

Treatment: Yes No Unknown

If yes, indicate what treatment was performed (choose all that apply):

Photocoagulation

Radiation

Enucleation

Other (list) _____

--Flat smooth-surfaced lesion: Yes No Unknown

If yes, indicate location: Right Left Bilateral Unknown

Symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Visual loss

Other (list) _____

Treatment: Yes No Unknown

If yes, indicate what treatment was performed: _____

--Mixed mulberry/flat smooth-surfaced lesion: Yes No Unknown

If yes, indicate location: Right Left Bilateral Unknown

Symptoms: Yes No Unknown

Subject name: First, Middle, Last _____

DOB: _____

If yes, indicate which symptom(s) present (choose all that apply):

- Visual loss
- Pain
- Hemorrhage
- Other (list) _____

Treatment: Yes No Unknown

If yes, indicate what treatment was performed (choose all that apply):

- Photocoagulation
- Radiation
- Enucleation
- Other (list) _____

Achromic Patch: Yes No Unknown

If yes, indicate location: Right Left Bilateral Unknown

Vascular Changes: Yes No Unknown

If yes, indicate location: Right Left Bilateral Unknown

Optic Nerve Atrophy: Yes No Unknown

If yes, indicate location: Right Left Bilateral Unknown

Papilledema: Yes No Unknown

If yes, indicate location: Right Left Bilateral Unknown

Is this related to Hydrocephalus: Yes No Unknown (If yes, complete the section found under the Neurology heading)

List details of signs, symptoms and treatments: _____

Visual Field Defects: Yes No Unknown

If yes, indicate location: Right Left Bilateral Unknown

Is cause for visual defect known: Yes No Unknown

If yes, list: _____

Has subject been prescribed vigabatrin: Yes No Unknown

If yes: Used in the past Currently used

Duration of vigabatrin therapy: _____ month(s) _____ year(s)

NON-RETINAL FINDINGS

Non-retinal Findings: Yes No Unknown

If yes, indicate the finding (choose all that apply)

- Strabismus
- Right Left Bilateral Unknown
- Other (list) _____

VIII. CARDIOLOGY

Has subject ever been evaluated by cardiologist for TSC finding: Yes No Unknown

If yes, for diagnostic purposes for treatment for both

Is subject currently followed by cardiologist: Yes No Unknown

ELECTROCARDIOGRAM

Has subject had an electrocardiogram (EKG): Yes No Unknown

If yes, what was subject's age at most recent exam: _____ month(s) _____ year(s)

What were the results:

- Unknown
- Normal
- Arrhythmia present (list) _____
- Other (list) _____

Did subject have symptoms related to abnormality found by EKG: Yes No Unknown

Subject name: First, Middle, Last _____

DOB: _____

If yes, indicate which symptom(s) present (choose all that apply):

- Tachycardia
- Irregular heart rhythm
- Shortness of breath
- Other (list) _____

Were symptoms related to EKG abnormality treated: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

- Medication (list current medication) _____
- Ablation: _____ month(s) _____ year(s)
- Other (list) _____

CARDIAC IMAGING

Echocardiogram

Was prenatal high-resolution echocardiogram performed: Yes No Unknown

If yes, indicate the result:

- Unknown
- Normal
- Abnormal
- Rhabdomyomata
- Other abnormalities (list) _____

Has subject had an echocardiogram post birth: Yes No Unknown

If yes, what was subject's age at most recent exam: _____ month(s) _____ year(s)

OTHER CARDIAC IMAGING

Has subject had any of the following imaging studies performed (choose all that apply):

Study	Subject's age at most recent exam Month(s) / year(s)
<input type="checkbox"/> Chest X-ray	_____ / _____
<input type="checkbox"/> Chest CT	_____ / _____
<input type="checkbox"/> Chest MRI	_____ / _____
<input type="checkbox"/> Other (list) _____	_____ / _____

If any of the above imaging studies were performed, complete the following section. If not, skip to section IX (Pulmonology)

CARDIAC FINDINGS

- Unknown
- Normal

If normal, how was result found: Echocardiogram Chest x-ray CT MRI Other _____

- Abnormal

If abnormal, check all that apply:

- Rhabdomyomata Result found by: Echocardiogram Chest x-ray CT MRI Other _____
- Coarctation of aorta Result found by: Echocardiogram Chest x-ray CT MRI Other _____
- Cardiac enlargement Result found by: Echocardiogram Chest x-ray CT MRI Other _____
- Other (list) _____

If any cardiac findings were identified above, complete the following section. If not, skip to section IX (Pulmonology)

Rhabdomyomata: Yes No Unknown

If yes, when was the finding discovered: Prenatal Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: Echocardiogram CT MRI Other _____

Location/Quantity/Size (provide as much detail as possible based on most recent and best quality imaging study):

Subject name: First, Middle, Last _____

DOB: _____

Total no. of lesions	Size and number in each range			
	<0.5 cm	0.5-1.0 cm	1.1-2.5 cm	>2.5cm
<input type="checkbox"/> RA*	_____	_____	_____	_____
<input type="checkbox"/> RV*	_____	_____	_____	_____
<input type="checkbox"/> LA*	_____	_____	_____	_____
<input type="checkbox"/> LV*	_____	_____	_____	_____
<input type="checkbox"/> AS*	_____	_____	_____	_____
<input type="checkbox"/> VS*	_____	_____	_____	_____

* RA-right atrium, RV-right ventricle, LA-left atrium, LV-left ventricle, AS-atrial septum, VS-ventricular septum

Did subject have symptoms related to rhabdomyomata: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

- Arrhythmia
- Cardiomegaly
- Heart failure
- Other (list) _____

Treatment related to rhabdomyomata: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

- Medication
- Surgical resection
- Other (list) _____

Was tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA):

Yes No Unknown

If yes, indicate location of bank and physician who banked the sample: _____

Coarctation of aorta: Yes No Unknown

If yes, when was the finding discovered: Prenatal Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: Echocardiogram CT MRI Other _____

Did subject have symptoms related to coarctation of aorta: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

- Cardiomegaly
- Hypertension
- Other (list) _____

Treatment related to coarctation of aorta: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

- Surgical resection
- Other (list) _____

Other cardiovascular abnormalities: Yes No Unknown

If yes, were any other cardiovascular abnormalities found: Yes No Unknown

If yes, list abnormalities found: _____

If yes, when was the finding discovered: Prenatal Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: Echocardiogram Chest X-ray CT MRI Other _____

Did subject have symptoms related to other abnormality: Yes No Unknown

If yes, list _____

Did subject have treatment related to other abnormality: Yes No Unknown

If yes, list: _____

IX. PULMONOLOGY

Has subject ever been evaluated by pulmonologist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both

Is subject currently followed by pulmonologist: Yes No Unknown

Subject name: First, Middle, Last _____

DOB: _____

RELEVANT PULMONARY HISTORY

Does subject have any chronic pulmonary disorders not necessarily related to TSC: Yes No Unknown

If yes, indicate all that apply:

- Asthma
- Emphysema
- Other (list) _____

Did subject have pulmonary signs or symptoms: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

- None
- Cough
- Chest pain
- Chylothorax
- Other (list) _____
- Shortness of breath
- Wheezing
- Pneumothorax

Has subject ever habitually smoked: Yes No Unknown

If yes, indicate how many years subject smoked: _____ years

What substance did subject smoke: Cigarettes Cigars Pipe Other _____

Does subject currently smoke: Yes No Unknown

If no, what is interval since last use: _____ month(s) _____ year(s)

How much does subject smoke and how often:

- Cigarettes How many/day: _____
- Pipe How many/day: _____
- Cigars How many/day: _____
- Other How many/day: _____

Pregnancy: Yes No Unknown N/A

If yes, Number of pregnancies: _____

Has subject reached menopause: Yes No Unknown N/A

Has subject undergone a hysterectomy: Yes No Unknown N/A

If yes, when was surgery performed: _____ year

Has subject undergone an Oophorectomy: Yes No Unknown N/A

If yes, when was surgery performed: _____ year

Hormone therapy (including birth control substances): Yes No Unknown N/A

Estrogen: _____ years taken

If yes, is subject currently taking Estrogen: Yes No Unknown

If no, what is interval since last use: _____ month(s) _____ year(s)

Progesterone: _____ years taken

If yes, is subject currently taking Progesterone: Yes No Unknown

If no, what is interval since last use: _____ month(s) _____ year(s)

Other (list): _____

Does subject have a family history of pulmonary disease: Yes No Unknown

If yes, give details: _____

PULMONARY PHYSICAL EXAM

Does subject have any of the following:

- Wheezes
- Crackles

Subject name: First, Middle, Last _____

DOB: _____

Clubbing of digits

Other (list) _____

PULMONARY LABS/STUDIES

(Provide most current lab values for all that apply:)

Test	Values	Date of most recent test results month / year
Pulmonary function test:	<input type="checkbox"/> Tested <input type="checkbox"/> Not tested	
FEV ₁	_____	____ / ____
FVC	_____	____ / ____
DLCO	_____	____ / ____
Arterial blood gasses	<input type="checkbox"/> Tested <input type="checkbox"/> Not tested	
PaO ₂	_____ mmHg	____ / ____
PACO ₂	_____ mmHg	____ / ____
pH	_____	____ / ____
Hemoglobin oxygen saturation test:	<input type="checkbox"/> Tested <input type="checkbox"/> Not tested	
Sa O ₂	_____ %	____ / ____

PULMONARY DIAGNOSTICS

Has subject had any of the following diagnostic studies performed (choose all that apply):

Study	What was subject's age at most recent exam month(s) / year(s)
<input type="checkbox"/> X-ray-Chest	____ / ____
<input type="checkbox"/> High resolution CT-Chest	____ / ____
<input type="checkbox"/> CT-Chest	____ / ____
<input type="checkbox"/> MRI	____ / ____
<input type="checkbox"/> Pulmonary Function Test (PFT)	____ / ____
<input type="checkbox"/> Biopsy-bronchoscopic	____ / ____
<input type="checkbox"/> Biopsy-surgical	____ / ____
<input type="checkbox"/> Other (list) _____	____ / ____
_____	____ / ____
_____	____ / ____

If any of the above diagnostic studies were performed, complete the following section. If not, skip to section X (Renal)

PULMONARY FINDINGS

If any of the above imaging studies were performed, what were the results: (choose all that apply)

Unknown

Normal

If normal, how was result found: X-ray High resolution CT CT MRI PFT Biopsy-bronchoscopic

Biopsy, surgical Other (list) _____

Abnormal

If abnormal, check all that apply:

Cystic lesions consistent with lymphangiomyomatosis (LAM)

Result found by: X-ray High resolution CT CT MRI PFT Biopsy-bronchoscopic

Biopsy, surgical Other (list) _____

Multifocal micronodular pneumocyte hyperplasia (MMPH)

Result found by: X-ray High resolution CT CT MRI PFT Biopsy-bronchoscopic

Biopsy, surgical Other (list) _____

Other (list) _____

Subject name: First, Middle, Last _____

DOB: _____

If any of the above pulmonary abnormalities were identified, complete the following section. If not, skip to section X (Renal).

Cystic lesions/LAM: Yes No Unknown

If yes, subject's age at time of discovery: _____ month(s) _____ year(s)

Result found by: X-ray High resolution CT CT MRI PFT Biopsy-bronchoscopic Biopsy-surgical
Other _____

Pathology comments, if relevant: _____

Location (based on most recent and best quality imaging study): Right Left Bilateral

Were any treatments performed: Yes No Unknown

If yes, choose the treatment performed:

Inhaler: List type _____ PRN use Scheduled use

O₂ supplementation: PRN use Scheduled use

Progesterone therapy

Lung transplant

Hysterectomy/oophorectomy

Chest tube placement: Right Left Bilateral

Chylous fluid drainage: Right Left Bilateral

Pleurodesis: Right Left Bilateral

Chest surgery: Right Left Bilateral

Other (list) _____

MMPH (Multifocal multinodular pneumocyte hyperplasia): Yes No Unknown

If yes, subject's age at time of discovery: _____ month(s) _____ year(s)

Result found by: X-ray High-resolution CT CT MRI PFT Biopsy Other _____

Pathology comments, if relevant: _____

Location (based on most recent and best quality imaging study): Right Left Bilateral

Other Findings: Yes No Unknown

If yes, list finding: _____

Subject's age at time of discovery: _____ month(s) _____ year(s)

Result found by: X-ray High-resolution CT CT MRI PFT Biopsy Other _____

Pathology comments, if relevant: _____

Did subject have signs or symptoms related to other abnormal pulmonary findings: Yes No Unknown

If yes, list findings: _____

Were any treatments related to other abnormal pulmonary findings: Yes No Unknown

If yes, list: _____

X. RENAL

Has subject ever been evaluated by nephrologist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both

Is subject currently followed by nephrologist: Yes No Unknown

Has subject ever been evaluated by urologist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both

Is subject currently followed by urologist: Yes No Unknown

RENAL PHYSICAL EXAM

Does subject have a palpable mass: Yes No Unknown

If yes: Right Left Bilateral Unknown

Does subject have any other relevant physical findings (list) _____

Subject name: First, Middle, Last _____

DOB: _____

RENAL LABS

(Provide most current lab values)

Labs	Values	Date of most recent test results month(s) / year(s)
<input type="checkbox"/> Creatinine <input type="checkbox"/> Not tested	_____	____ / ____
<input type="checkbox"/> BUN <input type="checkbox"/> Not tested	_____	____ / ____
<input type="checkbox"/> Urine protein <input type="checkbox"/> Not tested	<input type="checkbox"/> 1+ <input type="checkbox"/> 2+ <input type="checkbox"/> 3+ <input type="checkbox"/> 4+	____ / ____
<input type="checkbox"/> Hematuria <input type="checkbox"/> Not tested	<input type="checkbox"/> Trace <input type="checkbox"/> Small <input type="checkbox"/> Medium <input type="checkbox"/> Large	____ / ____

RENAL DIAGNOSTICS

Has subject had any of the following diagnostic studies performed (choose all that apply):

Study	What was subject's age at most recent exam month(s) / year(s)
<input type="checkbox"/> Ultrasound – Renal/Abdominal	____ / ____
<input type="checkbox"/> CT – Renal/Abdominal	____ / ____
<input type="checkbox"/> MRI	____ / ____
<input type="checkbox"/> Angiogram	____ / ____
<input type="checkbox"/> Nuclear study	____ / ____
<input type="checkbox"/> Biopsy	____ / ____
<input type="checkbox"/> Volumetric analysis of renal lesions	____ / ____
<input type="checkbox"/> Other (list) _____	_____

If any of the above diagnostic studies were performed, complete the following section. If not, skip to section XI (Neurology).

RENAL FINDINGS

Unknown

	Ultrasound	CT	MRI	Angiogram	Nuclear study	Other (list)
<input type="checkbox"/> Normal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
Kidney Size	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
Right: Length _____ cm		Width _____ cm	Thickness _____ cm			
Left: Length _____ cm		Width _____ cm	Thickness _____ cm			

Abnormal:

<input type="checkbox"/> Cystic lesions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Angiomyolipoma (AML)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Other solid tumor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Abnormal renal vasculature	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Other: _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____

If any of the above abnormalities were found, complete the following section. If not, skip to section XI (Neurology).

Cystic lesions: Yes No Unknown

If yes, when was the finding discovered: Prenatal Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: Ultrasound CT MRI Angiogram Nuclear study Other _____

Location/Quantity/Size (provide as much detail as possible based on most recent and best quality imaging study):

<input type="checkbox"/> Right	Total number of lesions: <input type="checkbox"/> 1-3 <input type="checkbox"/> 4-10 <input type="checkbox"/> >10	Size of largest cyst: _____ cm	or <input type="checkbox"/> Undetermined size
<input type="checkbox"/> Left	Total number of lesions: <input type="checkbox"/> 1-3 <input type="checkbox"/> 4-10 <input type="checkbox"/> >10	Size of largest cyst: _____ cm	or <input type="checkbox"/> Undetermined size

Subject name: First, Middle, Last _____

DOB: _____

Has subject ever had lesion which is no longer evident: Yes No Unknown

Radiology comments, if relevant: _____

Did subject have symptoms related to cystic lesions: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Elevated blood pressure

Hematuria

Pain

Impaired renal function

Other (list) _____

Were any treatments related to cystic lesions performed: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

Surgical resection: Right Left Bilateral

Nephrectomy: Right Left Bilateral

Dialysis

Renal transplantation

Other (list) _____

Was tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA):

Yes No Unknown

If yes, indicate location of bank and physician who banked sample: _____

Angiomyolipoma (AML): Yes No Unknown

If yes, when was the finding discovered: Prenatal Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: Ultrasound CT MRI Angiogram Nuclear study Biopsy Other _____

Pathology comments, if relevant: _____

Location/Quantity/Size (provide as much detail as possible based on most recent and best quality imaging study):

Right Total number of lesions: 1-3 4-10 >10 Size of largest AML: _____ cm or Undetermined size

Left Total number of lesions: 1-3 4-10 >10 Size of largest AML: _____ cm or Undetermined size

Did subject have symptoms related to AML: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

Elevated blood pressure Hematuria Pain Impaired renal function

Other (list) _____

Were any treatments related to AML performed: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

Surgical resection: Right Left Bilateral

Nephrectomy: Right Left Bilateral

Dialysis

Renal transplantation

Other (list) _____

Was tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA):

Yes No Unknown

If yes, indicate location of bank and physician who banked sample: _____

Other solid tumor: Yes No Unknown

If yes, when was the finding discovered: Prenatal Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: Ultrasound CT MRI Angiogram Nuclear study Biopsy

Other _____

Pathology comments, if relevant: _____

Location/Quantity/Size (provide as much detail as possible based on most recent and best quality imaging study):

Right Total number of lesions: 1-3 4-10 >10 Size of largest tumor: _____ cm or Undetermined size

Left Total number of lesions: 1-3 4-10 >10 Size of largest tumor: _____ cm or Undetermined size

Subject name: First, Middle, Last _____

DOB: _____

Did subject have symptoms related to other solid tumor: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

- Elevated blood pressure
- Hematuria
- Pain
- Impaired renal function
- Hemorrhage
- Other (list) _____

Were any treatments related to AML performed: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

- Surgical resection: Right Left Bilateral
- Nephrectomy: Right Left Bilateral
- Dialysis
- Chemotherapy
- Renal transplantation
- Other (list) _____

Abnormal renal vasculature: Yes No Unknown

If yes, when was the finding discovered: Prenatal Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: Ultrasound CT MRI Angiogram Nuclear study Other _____

Location of abnormal renal vasculature: Right Left Bilateral

Was abnormal renal vasculature found: Yes No Unknown

If yes, indicate type of finding (choose all that apply):

- Aneurysm
- Arteriovenous malformation
- Arterial dilatation
- Other (list) _____

Did subject have symptoms related to abnormal renal vasculature: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

- Elevated blood pressure
- Hematuria
- Pain
- Impaired renal function
- Hemorrhage
- Other (list) _____

Were any treatments related to abnormal renal vasculature performed: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

- Surgical resection: Right Left Bilateral
- Embolization: Right Left Bilateral
- Nephrectomy
- Other (list) _____

XI. NEUROLOGY

Has subject ever been evaluated by neurologist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both

Is subject currently followed by neurologist: Yes No Unknown

Has subject ever been evaluated by epileptologist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both

Is subject currently followed by epileptologist: Yes No Unknown

Has subject ever been evaluated by neurosurgeon for TSC finding: Yes No Unknown

Subject name: First, Middle, Last _____

DOB: _____

If yes: for diagnostic purposes for treatment for both
Is subject currently followed by neurosurgeon: Yes No Unknown

Has subject ever been evaluated by psychiatrist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both
Is subject currently followed by psychiatrist: Yes No Unknown

Has subject ever been evaluated by psychologist/neuropsychologist for TSC finding: Yes No Unknown

If yes: for diagnostic purposes for treatment for both
Is subject currently followed by psychologist/neuropsychologist: Yes No Unknown

NEUROLOGIC PHYSICAL EXAM (list abnormal findings only)

Cranial nerves:

- Papilledema
- Visual field defect
- Eye movement abnormalities
- Other (list) _____

Motor:

- Focal weakness
 - Monoparesis affecting: R upper R lower L upper L lower
 - Hemiparesis affecting: R upper R lower L upper L lower
 - Quadriparesis

Tone:

- Spasticity
- Rigidity
- Hypotonia

Abnormal movements:

- Dystonia
- Chorea/athetosis
- Tremor

Coordination:

List limb and finding: _____

Sensory:

List finding: _____

Reflexes:

- Absent
- Hypoactive
- Hyperactive
- Babinski: Unilateral Bilateral

Gait:

- Nonambulatory
- Hemiparesis
- Diplegia

Subject name: First, Middle, Last _____

DOB: _____

BRAIN

BRAIN DIAGNOSTICS (NEUROIMAGING)

Has subject had any of the following imaging studies performed (choose all that apply):

Study	If yes, what was subject's age at most recent exam? Month(s) / year(s)	
<input type="checkbox"/> CT – Head	_____ / _____	
<input type="checkbox"/> MRI - Head	_____ / _____	
<input type="checkbox"/> MR Angiography (MRA)	_____ / _____	
<input type="checkbox"/> PET Scan – Standard	_____ / _____	
<input type="checkbox"/> AMT – PET scan	_____ / _____	(alpha-[11C]methyl-L-tryptophan-PET Scan)
<input type="checkbox"/> SPECT	_____ / _____	
<input type="checkbox"/> Other (list) _____	_____ / _____	

If any of the above diagnostic studies were performed, complete the following section. If not, skip to the Epilepsy part of section XI (Neurology).

BRAIN FINDINGS

Unknown

	Results found by						
	CT	MRI	MRA	PET-Standard	AMT-PET	SPECT	Other
<input type="checkbox"/> Normal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Abnormal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Tubers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Radial glial white matter lesions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Subependymal nodules (SEN)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Subependymal giant-cell astrocytoma (SEGA)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Other _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Other _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____

If any of the above abnormal findings were identified, complete the following section. If not, skip to the Epilepsy part of section XI (Neurology).

Tubers

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: CT MRI Other _____

Location/Quantity/Size (include **ONLY** information on tubers identified by T2 or FLAIR MRI imaging):

Location	no. of lesions	Size and number in each range			Lesion type (choose all that apply)		
		<1.5 cm	1.5-3.0 cm	>3.0cm	Cortical	Subcortical	Cortical extending to subcortical
Frontal							
<input type="checkbox"/> Right	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Left	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Parietal							
<input type="checkbox"/> Right	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Left	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Temporal							
<input type="checkbox"/> Right	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Left	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Subject name: First, Middle, Last _____

DOB: _____

Occipital	<input type="checkbox"/> Right	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/> Left	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cerebellar	<input type="checkbox"/> Right	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/> Left	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diencephalon	<input type="checkbox"/> Right	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/> Left	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Brain stem	<input type="checkbox"/> Right	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/> Left	_____	_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Other: _____

Radial glial white matter lesions

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: MRI Other (list) _____

Location: Right hemisphere Left hemisphere

Subependymal nodules (SEN) (lesions < 1 cm)

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: CT MRI Other (list) _____

Location/Quantity/Size:

Location	Total # of lesions	Size and # in each range	
		<0.5 cm	0.5-0.9 cm
<input type="checkbox"/> Right lateral ventricle	_____	_____	_____
<input type="checkbox"/> Left lateral ventricle	_____	_____	_____

Subependymal giant cell astrocytoma (SEGA) (lesions 1 cm or larger)

When was the finding discovered: Prenatal Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: CT MRI Other _____

Location/Quantity/Size:

Location	Total # of lesions	Size and # in each range			
		1.0-2.0 cm	2.1-3.0 cm	3.1-5.0 cm	>5.0 cm
<input type="checkbox"/> Right frontal horn	_____	_____	_____	_____	_____
<input type="checkbox"/> Left frontal horn	_____	_____	_____	_____	_____
<input type="checkbox"/> Right posterior lateral ventricle	_____	_____	_____	_____	_____
<input type="checkbox"/> Left posterior lateral ventricle	_____	_____	_____	_____	_____

Did subject have symptoms related to SEGA: Yes No Unknown

If yes, indicate which symptom(s) present (choose all that apply):

- Hydrocephalus
- Ventriculomegaly
- Headaches
- Increased seizures
- Visual impairment
- Eye movement abnormalities
- Neuroendocrine dysfunction
- Behavioral disturbances
- Sleep disorders
- Other (list) _____

Were any treatments related to SEGA performed: Yes No Unknown

If yes, what treatment was performed (choose all that apply):

Surgical resection: Number of times surgery performed _____

Location of lesion resected: _____

Subject name: First, Middle, Last _____

DOB: _____

- Right frontal horn Left frontal horn Right posterior ventricle Left posterior ventricle
Lesion size at time of surgery _____
Was subject symptomatic at time of surgery: Yes No Unknown
What was extent of resection: Total Partial
If partial, what was size of residual SEGA post surgery:
 1.0-2.0 cm 2.1-3.0 cm 3.1-5.0 cm >5.0 cm
 Other (list) _____

Was blood or tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA):
 Yes No Unknown
If yes, indicate location of bank and physician who banked sample: _____

Were there surgical complications related to SEGA: Yes No Unknown
If yes, indicate which complication(s) present (choose all that apply):
 Memory loss
 Need for ventricular shunt
 Gait disturbance
 Syndrome of inappropriate ADH (SIADH)
 Other (list) _____

Has there been regrowth of SEGA at operative site: Yes No Unknown
If there have been multiple surgeries, was surgery for (choose all that apply):
 Reduction of same lesion
 Regrowth of same lesion
 Resection of new/different lesion

Has there been malignant transformation related to SEGA: Yes No Unknown
If yes, provide details of tumor type and treatment, if known: _____

EPILEPSY

Has subject ever had seizures: Yes No Unknown
If yes, continue with this part of Section XI (Neurology). If No or Unknown, skip to the Sleep part of Section XI (Neurology)

Has subject ever had infantile spasms: Yes No Unknown
If yes, continue with this part of Section XI (Neurology). If No or Unknown, skip to Current Seizure History part of Section XI (Neurology), if appropriate.

Infantile Spasms

Does subject currently have infantile spasms: Yes No Unknown
Subject's age of onset: _____ month(s) _____ year(s) Unknown
Seizure cluster duration: <1 min. 1-<2 min. 2-<5 min. 5-10 min. >10 min.
Seizure cluster frequency (check all that apply):

Current Seizure Frequency

- History of <3 seizures/lifetime
 Seizure free, requires antiepileptic drug or treatment
 1 – 3 seizures/year
 4 – 11 seizures/year
 1 – 3 seizures/month
 1 – 6 seizures/week
 1 or more seizures/day

Greatest Seizure Frequency

- History of <3 seizures/lifetime
 1 – 3 seizures/year
 4 – 11 seizures/year
 1 – 3 seizures/month
 1 – 6 seizures/week
 1 or more seizures/day

Current treatment for infantile spasms (check all that apply and list medication or treatment where appropriate):

- Single medication _____
 Medication combination _____
 Vagus nerve stimulator (VNS)

Subject name: First, Middle, Last _____

DOB: _____

- Ketogenic diet
- Epilepsy surgery (if checked, complete the separate Surgery section)
- Other (list) _____

Most effective treatment for infantile spasms (check all that apply and list medication or treatment where appropriate):

- Single medication _____
- Medication combination _____
- Vagus nerve stimulator (VNS)
- Ketogenic diet
- Epilepsy surgery (if checked, complete the separate Surgery section)
- Other (list) _____

Prior history of infantile spasms

Has subject ever had infantile spasms which have resolved: Yes No Unknown

Age of onset: _____ month(s) _____ year(s) Unknown

Age of cessation: _____ month(s) _____ year(s) Unknown

Most effective treatment for infantile spasms: _____

Current Seizure History

Does subject currently have seizures: Yes No Unknown

If yes, continue with this part of Section XI (Neurology). If No or Unknown, skip to Prior Seizure History.

Current seizure type:

Generalized Seizures

Partial Seizures

- Tonic clonic seizures (TC)
- Tonic seizures (T)
- Clonic seizures (C)
- Myoclonic seizures (M)
- Atonic seizures (A)
- Atypical absence seizures (AA)
- Typical absence seizures (TA)
- Other (GO) (list): _____

- Simple partial sensory (SPS)
- Simple partial motor (SPM)
- Complex partial seizures (CPS)
- Secondary generalized seizures (SG)
- Gelastic seizures (G)
- Other (PO) (list) _____

Other seizures

- Febrile seizures (F)
- Other (OO) (list) _____

Age of onset for current seizure type (use above abbreviation for seizure type). List all that apply:

Seizure Type	Age of Onset			Seizure duration				
	Month(s)	Year(s)	Unknown	<1 min	<2 min	<5 min	5-10 min	>10 min
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Frequency of seizures:

Current Seizure Frequency

Greatest Seizure Frequency

- History of <3 seizures/lifetime
- Seizure free, requires antiepileptic drug or treatment
- 1 – 3 seizures/year
- 4 – 11 seizures/year
- 1 – 3 seizures/month

- History of <3 seizures/lifetime
- 1 – 3 seizures/year
- 4 – 11 seizures/year
- 1 – 3 seizures/month
- 1 – 6 seizures/week

Subject name: First, Middle, Last _____

DOB: _____

1 – 6 seizures/week

1 or more seizures/day

1 or more seizures/day

Longest seizure-free duration (list) : _____ months _____ year(s)

Current treatment (check all that apply and list medication or treatment where appropriate):

Single medication _____

Medication combination _____

Vagus nerve stimulator (VNS)

Ketogenic diet

Epilepsy surgery (if checked, complete the separate Surgery section)

Other (list) _____

Most effective treatment for infantile spasms (check all that apply and list medication or treatment where appropriate):

Single medication _____

Medication combination _____

Vagus nerve stimulator (VNS)

Ketogenic diet

Epilepsy surgery (if checked, complete the separate Surgery section)

Other (list) _____

Prior seizure history

Has subject ever had a prior seizure type which has resolved: Yes No Unknown

If yes, list prior seizure type (use abbreviation list found under 'Current Seizure Type' page 21. List all that apply):

Seizure type	Age of onset		Age of cessation	
	Month(s)/Year(s)	Unknown	Month(s)/Year(s)	Unknown
_____	_____/____	<input type="checkbox"/>	_____/____	<input type="checkbox"/>
_____	_____/____	<input type="checkbox"/>	_____/____	<input type="checkbox"/>
_____	_____/____	<input type="checkbox"/>	_____/____	<input type="checkbox"/>
_____	_____/____	<input type="checkbox"/>	_____/____	<input type="checkbox"/>
_____	_____/____	<input type="checkbox"/>	_____/____	<input type="checkbox"/>
_____	_____/____	<input type="checkbox"/>	_____/____	<input type="checkbox"/>

Most effective treatment for prior seizure type (check all that apply and list medication or treatment where appropriate):

Single medication _____

Medication combination _____

Vagus nerve stimulator (VNS)

Ketogenic diet

Epilepsy surgery (if checked, complete the separate Surgery section)

Other (list) _____

Status Epilepticus

Has subject ever had status epilepticus (SE): Yes No Unknown

If yes, number of occurrences: _____

Number of emergency room (ER) visits due to SE (lifetime): _____

Number of hospitalizations due to SE (lifetime): _____

Past Medical Treatments

Medications (check all that apply):

Medications	Reason for discontinuation of medication		
	Adverse effect	Lack of efficacy	Seizure Remission
<input type="checkbox"/> ACTH	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Clonazepam	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Clorazepate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Diazepam	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Subject name: First, Middle, Last _____

DOB: _____

- | | | | |
|---|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> Ethosuximide | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Felbamate | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Gabapentin | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Lamotrigine | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Levetiracetam | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Lorazepam | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Oxcarbazepine | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Phenobarbital | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Phenytoin | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Prednisone | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Primidone | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Tiagabine | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Topiramate | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Valproic acid | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Vigabatrin | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Vitamin B ₆ | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Zonisamide | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other: _____ | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other: _____ | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other: _____ | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Other past treatments (check all that apply):

- Vagus nerve stimulator (VNS)
Reason discontinued: Adverse effect Lack of efficacy Seizure remission
Date VNS inactivated: _____ Date VNS removed: _____
Total length of treatment: _____ month(s) _____ year(s)

- Ketogenic diet
Reason discontinued: Adverse affect Lack of efficacy Seizure remission
Total length of treatment: _____ month(s) _____ year(s)

Epilepsy Surgery

Has subject had epilepsy surgery: Yes No Unknown

If yes, continue with this part of Section XI (Neurology). If No or Unknown, skip to Sleep part of Section XI (Neurology).

Age at time of surgery: _____ month(s) _____ year(s) Unknown

Type of surgery:

- Tuber resection
- Multiple tuber resection
- Temporal lobectomy
- Other lobectomy
- Hemispherectomy
- Corpus callosotomy
- Deep brain stimulation
- Other (list) _____

Presurgical evaluation:

- EEG
- Video EEG
- MRI
- SPECT
- WADA
- PET-Standard
- AMT-PET
- Other (list) _____

Surgical results (check all that apply):

- No benefit
- <50 % seizure reduction

Subject name: First, Middle, Last _____

DOB: _____

- 50-75 % seizure reduction
- 76-90 % seizure reduction
- 91-99 % seizure reduction
- Reduced seizure severity
- Reduced seizure duration
- Reduction in prior epilepsy treatment:
 - Polytherapy to monotherapy
 - AED dosage reduction
 - Discontinuation of AED
 - Removal of VNS device
 - Discontinuation of Ketogenic Diet
- Seizure remission

Surgical or post-surgical complications

- Hemorrhage
- Hydrocephalus with shunting
- Visual field change
- Facial weakness
- Motor weakness: Transient Persistent
- Infection
- Speech deficit
- Death
- Other (list): _____

SLEEP

Does subject have pervasive and persistent difficulties with sleep: Yes No Unknown

If yes, what are the main difficulties (check all that apply):

Poor quality (or non-restorative) sleep:

- Restless sleep
- Wakes up tired
- Wakes up in a bad mood
- Permanently drowsy during day
- Daytime naps

Anxieties about sleep:

- Afraid to go to bed
- Afraid of the dark
- Afraid of dying during sleep
- Insists on sleeping with someone else
- Needs security object
- Insists on bedtime rituals

Parasomnias:

- Talks in sleep
- Walks in sleep
- Nightmares
- Sleep terrors
- Teeth grinding
- Head banging

Disordered breathing:

- Snoring
- Gagging or choking
- Apnoeic (cessation of breathing) episodes

Early waking:

- Early morning wakening (before 0500)

Other:

- Narcolepsy
- Cataplexy
- Other _____

Subject name: First, Middle, Last _____

DOB: _____

Other _____

Has subject ever had a polysomnogram (PSG): Yes No Unknown

If yes, what was the subject's age at most recent exam: _____ month(s) _____ year(s)

If a PSG was conducted, what were the results?

Unknown

Normal

Abnormal (check all that apply):

Obstructive sleep apnea

Central sleep apnea

Frequent arousals

Restless legs

Snoring

Seizures

Terminal insomnia

Findings suggestive of narcolepsy

Other _____

Other _____

Other _____

Other _____

Has subject ever received treatment for sleep disorder: Yes No Unknown

If yes, check all that apply:

Current treatments

Previous treatments

Medications

Melatonin

Diphenhydramine

Imipramine

Amitriptyline

Trazodone

Chloral hydrate

Benzodiazepines

Other _____

Non-invasive ventilation (e.g., CPAP, BiPAP, etc.)

Oral appliance for sleep disorder (e.g., Bruxism, snoring, etc.)

Surgical intervention (e.g., adenoidectomy, tonsillectomy, deviated septum repair, etc.)

Medications

Melatonin

Diphenhydramine

Imipramine

Amitriptyline

Trazodone

Chloral hydrate

Benzodiazepines

Other _____

Non-invasive ventilation (e.g., CPAP, BiPAP, etc.)

Oral appliance for sleep disorder (e.g., Bruxism, snoring, etc.)

Surgical intervention (e.g., adenoidectomy, tonsillectomy, deviated septum repair, etc.)

OTHER NEUROLOGICAL ABNORMALITIES

Were any other neurological abnormalities found: Yes No Unknown

If yes, check all that apply:

Chordoma

Meningioma

Other (list): _____

Result found by (indicate diagnostic tool): CT MRI MRA PET-standard AMT-PET SPECT

Other (list): _____

Did subject have symptoms related to other abnormality: Yes No Unknown

If yes, list: _____

Did subject have treatment for the findings indicated above: Yes No Unknown

If yes, briefly describe: _____

Subject name: First, Middle, Last _____

DOB: _____

XII. OTHER ORGAN INVOLVEMENT

LIVER

LIVER DIAGNOSTICS

Has subject had any of the following diagnostic studies performed (choose all that apply):

- US-liver/abdominal
- CT-liver/abdominal
- MRI
- Other (list): _____

If any of the above diagnostics were performed, complete the following section. If not, skip to the Other Organs part of section XII (Other Organ Involvement).

LIVER FINDINGS

If any of the above imaging studies were performed (ultrasound, CT, MRI, angiogram, nuclear study) what were the results:

Unknown

	Results found by					
	CT	MRI	Angiogram	Nuclear study	Other (list)	
<input type="checkbox"/> Normal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Abnormal:						
<input type="checkbox"/> Hamartoma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Single lesion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
<input type="checkbox"/> Multiple lesions:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____
How many: _____ Diameter of largest lesion: _____ cm						
<input type="checkbox"/> Other: _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> _____

Did subject have symptoms: Yes No Unknown

If yes, describe: _____

Did subject receive treatment: Yes No Unknown

If yes, indicate treatment received: _____

OTHER ORGANS

Did subject have other organ involvement: Yes No Unknown

If yes, check all that apply:

- Thymus
- Fibromatous tumors of pharynx, larynx, esophagus
- Stomach tumors
- Duodenum tumors
- Colon/rectum polyps/tumors
- Pancreas
- Spleen
- Gall bladder
- Lymph nodes
- Bone
- Other _____
- Other _____
- Other _____

Briefly describe findings indicated above: _____

Subject name: First, Middle, Last _____

DOB: _____

Did subject have treatment for the findings indicated above: Yes No Unknown

If yes, briefly describe: _____

XIII. GENDER SPECIFIC CONCERNS

FEMALE (if applicable)

Puberty

If subject has underage adrenarche (secondary sex characteristics), was it on time (age 6 – 8 years): Yes No Unknown

If no, was it Early Late

If subject has undergone thelarche (breast development), was it on time (age 9-13): Yes No Unknown

If no, was it Early Late

If subject has undergone menarche (menstruation), was it on time (age 10-15): Yes No Unknown

If no, was it Early Late

Hormone Therapy

Has subject ever had female hormonal therapy (e.g., birth control, hormonal replacement therapy, etc.): Yes No Unknown

If yes, is subject being currently treated: Yes No Unknown

If yes, list any medications: _____

Pregnancy

Has subject ever been pregnant: Yes No Unknown

If yes, number of pregnancies _____

Were there complications: Yes No Unknown

If yes, indicate which complications occurred:

Maternal gestational diabetes

Maternal infection

Maternal seizures

Maternal substance abuse

Premature rupture of membranes

Premature birth

Other (list): _____

Did subject have any miscarriages or stillbirths: Yes No Unknown

If subject delivered liveborn young, were there congenital anomalies: Yes No Unknown

If yes, how many children were affected? _____ (list below)

Affected child	Anomalies	Mild	Moderate	Severe
Child 1	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Child 2	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Child 3	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Child 4	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Reproductive System

Has subject had any reproductive system findings: Yes No Unknown

If yes, check all that apply:

Subject name: First, Middle, Last _____

DOB: _____

Type of finding	Is the finding related to TSC?		
<input type="checkbox"/> Ovarian tumor	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
<input type="checkbox"/> Uterine tumor	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
<input type="checkbox"/> Other (list): _____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
<input type="checkbox"/> Other (list): _____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
<input type="checkbox"/> Other (list): _____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown

Menopause
 Has subject undergone menopause: Yes No Unknown
 If yes, was it: natural or secondary to _____ Oophorectomy/hysterectomy

MALE (if applicable)

Puberty
 If subject has entered puberty, was it on time (age 9 - 15 years): Yes No Unknown
 If no, was it Early Late
 Has subject fathered children: Yes No Unknown
 If subject delivered liveborn young, were there congenital anomalies: Yes No Unknown
 If yes, how many children were affected? _____ (list below)

Affected child	Anomalies	Mild	Moderate	Severe
Child 1	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Child 2	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Child 3	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Child 4	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Reproductive System
 Has subject had any reproductive system findings: Yes No Unknown
 If yes, check or list if applicable:

Type of finding	Is the finding related to TSC?		
<input type="checkbox"/> Testicular tumor	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
<input type="checkbox"/> Other (list): _____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown

XIV. OTHER MEDICAL/SURGICAL HISTORY

MEDICAL

Has subject had any significant medical conditions not related to TSC: Yes No Unknown
 If yes, list condition, and check whether condition is active:

Condition	Active	Medication	Other Treatment
_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____
_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____
_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____
_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____

Subject name: First, Middle, Last _____

DOB: _____

_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	_____	_____
_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	_____	_____
_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	_____	_____
_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	_____	_____
_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	_____	_____
_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	_____	_____

SURGICAL

Has subject had any surgery procedure not related to TSC: Yes No Unknown

If yes, list: _____

Tuberous Sclerosis Complex (TSC) National Database (DB)
Annual Report – W81XH-04-0896
PI: Dr. Steven Sparagana

Appendix G – Mortality Report Tool

**Tuberous Sclerosis Complex (TSC) Database
Data Collection Form -- Mortality Report**
(Please print all information and check appropriate responses)

Today's Date (mm/dd/yyyy): ____ / ____ / ____

Subject's Full Name (first/middle/last): _____

Age: _____ Date of Birth (mm/dd/yyyy): ____ / ____ / ____ Date of Death (mm/dd/yyyy): ____ / ____ / ____

Was death related to complications of TSC: Y N U

If yes, please check category and describe (e.g. heart failure due to rhabdomyoma):

- Cardiac _____
- LAM _____
- Renal _____
- Brain lesions other than epilepsy _____
- Epilepsy _____
- Other _____

If cause of death was not related to TSC, please choose category and briefly describe (e.g., motor vehicle accident)

Accidental causes: _____
Other (please list): _____

Was an autopsy performed: Y N U

If yes, where: _____ city _____ state

Is autopsy report available: Y N U

Were any organs donated to a tissue bank (e.g., TSC Tissue Donation Program at TSA) : Y N U

If yes, please indicate name and location of bank and physician who banked samples: _____

Comments: _____

For Center Use Only

Database ID:	TSC Consortium Site:	Medical Record #:
DB Consent: <input type="checkbox"/> Y <input type="checkbox"/> N	Form completed by:	Registry: <input type="checkbox"/> Y <input type="checkbox"/> N

Appendix H – Aims and Hypotheses

Focused Hypotheses (November 2004 Meeting Results)

Topics:

- Variability of disease
- Inter-relationship of manifestations
- Genotype-phenotype

Specific areas of interest:

Brain
Kidney

Representative Research Questions:

Is there a predictable inter-relationship of the manifestations of TSC?

- What is the relationship between seizures, tubers and other cerebral malformations on cognitive behavioral outcome?
 - Are there regression syndromes?
 - What are the types of neuro-psychiatric problems that occur in TSC?
 - Treatments
 - ADHD
 - Learning Disability/MR
 - Autism spectrum disorder
 - Obsessive compulsive disorder
 - Depression/Bipolar disease/Anxiety
 - Sleep Disorders
 - New onset of psychiatric diagnosis in adults?
- Is there any correlation between skin manifestations and other features?
- Presence of retinal TSC lesions?
 - Yes, no, not assessed
- Seizures
 - Yes, no, age of onset, resolution of
 - Type
 - Infantile spasm
 - Generalized
 - Partial
 - Triggers
 - Severity/frequency
 - History of status epilepticus
 - Treatments
 - VNS
 - Ketogenic Diet
 - AEDs

Tuberous Sclerosis Complex (TSC) National Database (DB)

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PI: Dr. Steven Sparagana

- Surgery
 - Resective
 - Corpus Callosum
 - Deep Brain Stimulation
- Electroencephalogram
 - Type of study
 - Normal/Abnormal
 - Slowing
 - Focal discharges
 - Multifocal discharges
 - Hypsarrhythmia
 - Generalized
- Brain lesions
 - How many, where, CT vs MRI (equipment)
 - Tubers
 - Subependymal nodules
 - SEGA
 - Migration defects
- Is there a higher incidence of endocrine disease in TSC patients?
 - Diabetes
 - Weight/obesity
 - Thyroid or other endocrinopathy
 - Growth and hemihypertrophy
- If you have heart lesions could you have other vascular lesions?
 - Does the presence of rhabdomyoma put the patient at higher risk for cerebral or cerebral vascular disease?
 - Presence of arrhythmia?
 - Potential precipitators
 - Age of onset
- What is the relationship between renal AMLs, liver lesions or other abdominal lesions?
 - Presence of AMLs
 - Number of AMLs
 - Size of AMLs

Does genotype predict phenotype and offer prognostic information?

- TSC1
- TSC2
- Mutation type
- Genotype
- Modifying genes
- Sex influence
- Environmental modifiers
 - Socioeconomic status
 - Diet

Tuberous Sclerosis Complex (TSC) National Database (DB)

Annual Report – W81XH-04-0896

PI: Dr. Steven Sparagana

Given a large enough cohort of individuals with TSC followed for a prolonged period of time, can we precisely define the range of clinical variability?

- How large is large enough?
- What are the unique problems of TSC in the adult?
 - Cardiac disease
 - Stroke
 - Dementia
 - Cause of death/age
- Duration?
- What factors of TSC are influenced by the age of the patient/s?
 - Biochemical changes/hormones
 - Puberty
 - Menstruation
 - Menopause
 - Pregnancy outcome
 - Is there a higher rate of complications for TSC moms?
 - Is there a higher rate of congenital anomalies of offspring?
 - Hormone based contraceptives of any type/HRT
 - ACTH
- How do treatment attempts affect clinical variability?
- Can we predict tumor growth?

Abbreviations:

ACTH	Adrenocorticotrophic Hormone
ADHD	Attention Deficit Hyperactivity Disorder
AED	Anti-Epileptic Drug
AML	Angiomyolipoma
CT	Computed Tomography
HRT	Hormone Replacement Therapy
MRI	Magnetic Resonance Imaging
MR	Mental Retardation
TSC	Tuberous Sclerosis Complex
VNS	Vagus Nerve Stimulator

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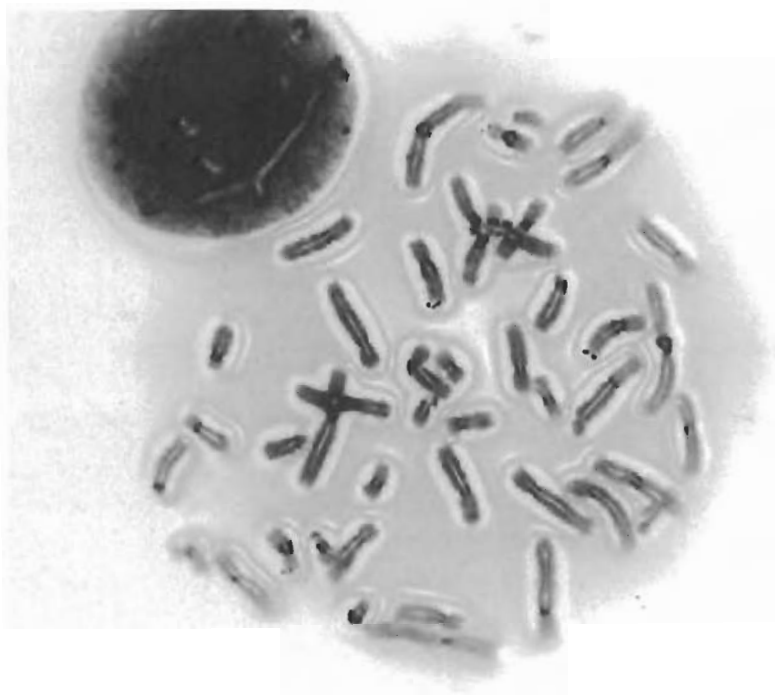
PI: Dr. Steven Sparagana

Appendix I – TSC/LAM International Research Symposium program/abstract



Tuberous Sclerosis Alliance

**TSC/LAM
International Research
Symposium**



April 8-10, 2005 • Cincinnati, Ohio

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NEUROLOGICAL
DISORDERS AND STROKE



Office of
Rare
Diseases

National
Institutes
of Health

Clinical Features and Natural History of TSC

Steven P Sparagana and E. S. Roach

Department of Neurology, Texas Scottish Rite Hospital for Children and the University of Texas Southwestern Medical Center (Dr. Sparagana) and the Department of Neurology and Comprehensive Epilepsy Center, Wake Forest University School of Medicine, Winston-Salem, NC (Dr. Roach)

We will use the consensus diagnostic criteria for tuberous sclerosis complex (TSC) as the framework to review many of the common clinical features of TSC and their natural history. The major cutaneous findings of TSC include facial angiofibromas, unguinal fibromas, hypomelanotic macules (which occur in over 90% of the individuals with TSC), and the shagreen patch. Retinal hamartomas occur in up to 75% of individuals with TSC but; these are sometimes useful in establishing the diagnosis but do not typically cause clinically significant deterioration of vision. Cardiac rhabdomyomas occur in about two thirds of neonates with TSC and can be lethal in babies whose cardiac output is compromised; after the neonatal period, however, rhabdomyomas tend to shrink and do not typically become symptomatic aside from the occasional older person who develops a cardiac arrhythmia. Renal angiomyolipomas (AMLs) are present in about 75% of individuals with TSC by age 10 years but seldom cause symptoms before adolescence or adulthood. These renal tumors typically enlarge very slowly, and it is unusual for an AML to cause symptoms before adulthood, although renal AMLs are said to be the most common cause of death among adults.

Over 90% of the TSC patients in some series have epileptic seizures, although these do not always continue indefinitely and the seizures are not always intractable to medical or surgical management. Some individuals with epilepsy due to TSC are even able to successfully discontinue antiepileptic medication. The frequency of mental retardation has clearly been overestimated in previous years. Some estimates suggest that about half of the individuals with TSC have significant cognitive impairment, although some people without mental retardation will nevertheless have significant behavioral issues that are attributable to TSC. Giant cell astrocytomas occur in about 10% of the patients with TSC. Almost all of the giant cell tumors occur in children and are located near the anterior horn of the lateral ventricles. If detected early, giant cell tumors can be surgically removed with good results.

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Appendix J – Letter from Tuberous Sclerosis Alliance (Nancy Taylor)



801 Roeder Road, Suite 750
Silver Spring, MD 20910

Toll free: (800) 225-6872

Phone: (301) 562-9890

Fax: (301) 562-9870

www.tsalliance.org

E-mail: info@tsalliance.org

September 21, 2005

Dear Friends:

I'm writing to update you with some exciting news about the Tuberous Sclerosis Complex (TSC) Clinical Database project. I'm pleased to announce that the project is continuing its forward momentum with the TS Alliance assuming responsibility to develop and maintain the database. On behalf of the TS Alliance Board of Directors and the TSC Clinics across the country, I want to thank Texas Scottish Rite Hospital for Children for coordinating initial efforts on the database project. I also want to acknowledge the input from all members of the TSC Clinical Database Consortium. The initial work on the database has proven to be invaluable.

"We at Texas Scottish Rite Hospital for Children are grateful and honored to have played a significant role in the establishment of the Tuberous Sclerosis Complex Clinical Consortium and in the initial efforts to create a Tuberous Sclerosis Complex (TSC) Clinical Database. The collaboration between members of the TSC clinical research community and the TS Alliance has been fruitful," said Steven P. Sparagana, M.D., TSC Clinic Director at Texas Scottish Rite Hospital for Children and Principal Investigator of the DOD-funded TSC Natural History Study Development Award. "We applaud the TS Alliance's initiative to house the database, and we are ready and willing to transfer the task of database development and construction back to them. Our intent is to continue working with the TS Alliance and the Consortium to make the database a reality. These efforts will help all of us not only understand the nature of TSC better, but will also ultimately serve the fundamental purpose of helping to improve the lives of those affected by TSC."

Briefly, the TSC Clinical Database Project will allow the TS Alliance to enable and support research based on a vast array of data stored in a comprehensive information repository. All TSC Clinics will be invited to participate in collecting information that will provide valuable data on how TSC affects individuals throughout their lifespan – from birth to death. The database will incorporate the full range of TSC clinical information, combine data collected from multiple sources and, for the first time, make that information available to researchers. To be successful, the project will require collecting information from large numbers of individuals with TSC, including the complete range of symptoms (the phenotype) along with associated genetic (genotype) and demographic data.

The TS Alliance has contracted with Michael Cinkosky of Tesuji, Inc., to create the database. Michael has been leading teams that design and build software for biomedical laboratory and clinical research for more than 20 years. His team at Tesuji, Inc. has worked together on various projects ranging from commercial software applications to custom databases for both not-for-profit and commercial organizations.

Jo Anne Nakagawa will facilitate the project internally for the TS Alliance. She joined our staff as Director of Clinical Projects in August after working at UCLA in basic and clinical research for more 30 years. She has more than 15 years experience in clinical trials coordination in the Division of Pediatric Neurology. Her experience includes managing several physician-initiated investigational new drug (IND) studies such as the only U.S. multi-center vigabatrin study for patients with infantile spasms, which was conducted from 1996 to 2001. Jo Anne also will serve as our organization's liaison to the TSC Clinics; collaborate with TSC researchers, advisors, board members and staff; facilitate data sharing; and develop outreach programs to engage clinical science researchers to advance identifying treatments and the cure for TSC.

I will keep you informed as the project develops. In the meantime, if you have any questions, please free to contact me via email at ntaylor@tsalliance.org or call me at (800) 225-6872.

Regards,

A handwritten signature in cursive script that reads "Nancy Taylor".

Nancy L. Taylor, CEO

A national non-profit organization dedicated to research, education and support.

Mission statement: Tuberous Sclerosis Alliance is dedicated to finding a cure for tuberous sclerosis while improving the lives of those affected by TSC. Page 62 of 191

Tuberous Sclerosis Complex (TSC) National Database (DB)
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Appendix K – Tesuji, Inc. Development Plan

Tuberous Sclerosis Alliance TSC Clinical Database

Project Definition

This Project Definition describes the scope, goals, and expectations for the Tuberous Sclerosis Complex (TSC) Clinical Database project for the Tuberous Sclerosis Alliance (TSA).

Motivation

This project will construct a central research repository for detailed information about patients with Tuberous Sclerosis Complex (TSC), a debilitating condition that affects some 50,000 Americans and perhaps one million people worldwide.

At present, a central information resource about TSC patients does not exist. Researchers who study the condition must attempt to obtain patient records from individual hospitals and clinics, or use their own records. In either case, gathering consistent and comprehensive information about more than a handful of patients is difficult or impossible for many involved in research in this area. This lack of a comprehensive information resource is limiting the types and scale of research projects that can be undertaken in this field.

To be successful, these research efforts require specific information about large numbers of patients. These data include the complete range of symptoms (phenotypes) along with associated genotype and demographic data. Studying these patterns along with patient histories and their responses to various diagnosis and treatment methods would enable researchers to improve clinical care. This will also help us gain a much better understanding of the disease mechanisms — essential to someday finding a cure.

The TSC Clinical Database Project will allow the Tuberous Sclerosis Alliance (TSA) to enable and support this kind of much needed research. By having a system that can handle the full range of TSC patient data, the TSA will be prepared to collect and combine patient data from multiple sources and, for the first time, make that critical information available in a useful form to researchers.

Scope

For this project we will develop the following components:

Database

The database will store information on TSC patients. In addition to general demographic information, the database will include detailed information some or all of the following areas:

- Neurology
- Dermatology
- Cardiology
- Behavior, Cognition, and Psychiatry
- Epilepsy and EEG
- Genetics
- Renal
- Imaging
- Medical History and Family History
- OB/GYN/Reproductive Issues

The final selection of areas of focus, and the exact content of the database in each of these areas, will be determined in collaboration with the TSA staff and working groups organized by the TSA and including physicians and researchers working in each area.

This will be a password-protected, relational database, maintained on a secure server.

Data Entry and Editing Interface

An easy-to-use, cross-platform, web-based interface will allow for secure data entry and editing by TSA staff. These users will be able to access this

interface from anywhere with an Internet connection, enabling them to work in most clinical environments. All communication of data using this interface will be encrypted, preventing unauthorized access.

This interface will be available to TSA staff only.

Data Reporting and Exporting Interface

The system will include a basic data reporting interface that will enable TSA staff to easily generate summary statistics about the contents of the database, and to export data subsets for use in research projects.

Administration Tools

The system will include an interface for routine administrative tasks such as user account creation, account removal, and access privilege adjustments. There will also be an automated backup system for routinely producing archive copies of the database.

Exclusions

For clarity, we list here several areas of functionality that will not be considered within the scope of this project.

No Data Analysis Tools

The system will not include data analysis features. Instead, people who desire to perform analysis on data in this system will make use of export files that can be read by various data analysis tools.

No Data Entry

This project covers only the design and creation of the database and supporting software, not the population of the database. This work will be performed by TSA staff, or other people acting on behalf of the TSA.

No Automated Data Entry Tools

The system will not include any automated data entry tools for directly importing data from other systems. This means, for example, that data from individual medical records will need to be entered into this system manually, even if that data appears in an electronic medical record.

No Development of Questionnaire

The TSA may choose to use a questionnaire to collect data in hardcopy form, rather than entering

data directly on-line. Design and production of such a questionnaire is outside the scope of this project.

Intended Users

The system is intended to be used by several different types of users. It is important that each of these groups be represented during the analysis and design of the system.

TSA Data Collection and Curation Staff

At the discretion of TSA, certain staff members will be granted access to the system in order to enter collected patient data, generate reports, and share data with researchers.

TSA Management

Some TSA managers may use the system only for generating data summary reports and for tracking the data collection process.

TSA System Administrator

At least one person must act as a system administrator to perform maintenance functions such as setting up user accounts and assigning user access privileges.

Other Affected Individuals

There are other groups of people who, while not direct users of the system, will be affected by its development and therefore should have influence on its development. This includes:

TSC Patients

Given that the purpose of the system is to track detailed medical information about TSC patients, they obviously represent an essential constituency that must be represented during the analysis and design process.

The TSC Research Community

This system will be designed to support the researchers who will use the data it contains. Researchers must be consulted to be sure that their needs are addressed in the analysis and design. This includes both the scope of the data to be collected, and the form in which it will be distributed to approved research projects.

General Requirements

There are several high-level requirements that the system must satisfy.

The system must be extensible

The system must be easily extended to accommodate new data types should they become needed at any time in the future.

The system must be secure

Access to the system must be password-controlled, and all data communication must be encrypted to prevent unauthorized access. The system must support several levels of access permission so that users can be granted access only to the functionality and data that they require to perform their jobs.

The user interface must be platform-neutral

The user interface must be platform-neutral, such that its use will not require a particular web browser or operating system.

Use of web-related communications protocols.

The user interface shall rely only on standard web-related communication protocols (e.g., http, https) to reduce the possibility that its use would conflict with firewalls or other security measures in place in clinics.

Assumptions

We are making the following assumptions, all of which are important for the success of this project:

The TSA will assemble a steering committee.

In order to make effective decisions quickly throughout the course of this project, it is essential that there be a relatively small group of people (e.g., 5 - 10) who have the authority to make decisions about the design and development of this project. We are assuming that the TSA will assemble this group at the beginning of the project and that it will remain intact throughout the entire project. This group will be required to review documents, meet occasionally (either in person, or by telephone), and represent all of the intended users and other people who will be affected by this project.

TSA staff will be available to answer questions.

TSA staff will be available as critical information resources for Tesuji for the duration of the project. This includes availability for occasional in-person interviews, telephone conversations or conference calls, and timely email exchanges.

TSA staff will facilitate communication between Tesuji and the working groups.

Efficient communication with the working groups to obtain information and approval of documentation and designs will be essential to the timely completion of this project. Tesuji will depend on TSA staff to facilitate this interaction.

All prior working group documentation will be available.

We will need all current, relevant documentation from the various working groups so that we do not need to begin from scratch on the analysis process – something that would certainly frustrate at least some members of these working groups.

TSA will obtain whatever regulatory and legal approvals are required for the implementation and operation of the system.

The operation of a database system that will contain medical records may be subject to certain regulatory restrictions. It is the responsibility of the TSA and their counsel to ensure that any required Institutional Review Board approval is obtained and that any special regulatory requirements are communicated to Tesuji as early as possible in the design process.

Technology selection

The system will be constructed using the following technology:

- Java Server Pages (JSPs),
- the open-source MySQL database, and
- the WebObjects development environment and application server.

There are no licensing fees for any of these components.

Tesuji will provide system hosting.

Although the system will be designed to be hosted anywhere, we will proceed under the assumption that, for simplicity and ease-of-support, Tesuji will provide hosting services at the time of deployment

and provide ongoing hosting services for a negotiated fee.

Constraints

No constraints have been identified at this time.

Deliverables

During this project we will deliver:

System Design Documentation

Tesuji will deliver to the TSA the following system design documentation:

- At the end of the Analysis Phase, the documentation will include a detailed domain model, including all information to be tracked by the final system, and workflow models showing how the system will be used.
- At the end of the Design Phase, the documentation will include: the database schema and annotated images of all important user interface screens.

The contents of all of the system design documentation will be subject to TSA approval.

The Deployed System

We will provide a deployed, installed, configured, and fully running system that meets the specifications in the System Design Document.

User Guide

A concise, easy-to-follow user guide will be provided for system users.

Training

We will provide up to two full days of user training at any site of TSA's choosing near the time of the delivery of the final system.

Source File Archive

All source code, libraries, installation tools, and instructions will be provided electronically so that the TSA will have everything it needs to modify and/or redeploy the system if it chooses to do so at some future date. Although we would hope to be involved in any future development, we believe TSA should have all options available.

Risks

It's important to keep in mind the risks associated with any endeavor — this helps identify and resolve problems early, so that the project can be completed as quickly and as efficiently as possible.

Access to Required Information

Access to people and information needs to be timely, efficient, and, when decisions need to be made, definitive. Poor access/availability can slow down development and delay completion.

Community Acceptance

Ultimately the success of this project depends on researchers getting the information they need to help the people with Tuberous Sclerosis Complex. This means the research community must be "on board" with this endeavor both during development (to ensure we are giving them what they need) and after deployment (to ensure they actually use it). Community acceptance must be a fundamental driving force guiding every aspect of development.

Regulatory Approval

If the TSA is required to obtain, for example, Institutional Review Board approval for this project, there is a risk that this approval will not be obtained. Lack of any required approval would jeopardize the entire project.

TSC Patient and Family Acceptance

Medical data can only be collected on patients who freely consent. Anything that limits the rate of patient consent would have a negative effect on the overall success of this project.

Tuberous Sclerosis Complex (TSC) National Database (DB)
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Appendix L – DB User Interface

User Interface Design

This chapter presents the interface design, which shows how the software will appear and function on the computer screen.

WHAT IS THE USER INTERFACE?

The User Interface (UI) is what is visible to users on the computer screen. Onscreen text, buttons, menus, windows, and images are all part of the UI. The UI design shows how users perform the specific functions described in the Workflow Analysis and how the software meets the requirements described in the Domain Analysis.

In this chapter we present the UI design primarily through a series of screenshots arranged to represent different points along typical, representative workflows. In practice, users may access these screens in a different order depending on their particular goals.

These screenshots show all elements that would be available to a user with the highest level of permissions, namely a TS Alliance administrator. Some screens, particularly those containing administrative functions, might not be accessible by other users.

All data shown in the screenshots are sample, representative data designed to illustrate various software functions; no actual patient data is displayed.

We present the UI in the following sections:

- Conventions
- Logging In
- Viewing and Entering Participant Data
- Creating New Participants
- Administration
- Printing Forms
- Reporting
- Help
- Messages

CONVENTIONS

Some design elements appear consistently throughout the user interface. These elements represent some common functions as described below.

Participant Data Tabs

Users view and edit all Participant data via seven “tabs” that group a Participant’s data into logical categories. The Background, Family, and Prenatal tabs present a simple list of data with an Edit button in the upper right corner (as shown below); clicking Edit makes all of the fields editable. The tabs allow users to view or enter Participant data in any order.



Ordering Table Data by Column

Whenever data are presented in tabular format, the rows can be ordered alphanumerically by clicking on any of the column headings; clicking a second time reverses the order. The column by which the data are currently sorted remains highlighted.

	Start	Stop	Treatment	Entered	Diagnoses
▶+	12 Feb 2006	12 Feb 2006	Excision	14 Mar 2006	Tumor
▶+	31 Jan 2006	31 Jan 2006	Resection-left	14 Mar 2006	Cystic Lesion
▶+	22 Apr 2005	Current	Clozapine	23 May 2006	None
▶+	22 Apr 2005	15 Jan 2006	Lithium	22 Jun 2006	Acute Stress Disorder

Details Boxes within Tables

Most data tables contain rows that can be expanded to show additional detail. Clicking the expansion triangle on the left end of a row shows and hides the details box for any row. A red + next to an expansion triangle indicates that the details box contains more information than that shown in the unexpanded row (such as text comments). Users must expand a row to make changes. Accordingly, every details box includes an Edit button in the upper right corner that makes all of the fields within the box editable. A Delete button in the upper left allows users to delete a row via a confirmation dialog (not shown).

▶+	22 Apr 2005	Current	Clozapine	23 May 2006	None
▶+	22 Apr 2005	15 Jan 2006	Lithium	22 Jun 2006	Acute Stress Disorder
▼	02 Jan 1997	23 Oct 1999	Quinidine	10 Aug 2006	Rhabdomyoma

Delete
Edit

Treatment Quinidine

Start Date 02 Jan 1997

Stop Date 23 Oct 1999

Adding New Rows to Tables

Most data tables include an Add New button in the upper left.

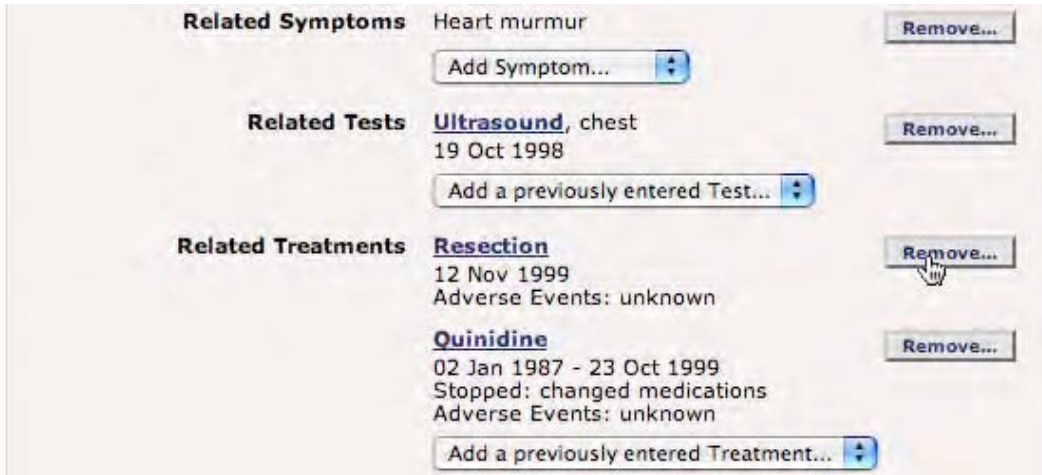
Add New Test						Show all details
						Hide all details
Date	Test	Area	Entered	Diagnoses	Images	
▶+ 08 Feb 2001	CT	Head	12 Sep 2007	None	27	
▶+ 08 Feb 2001	EKG	N.A.	24 Jan 2007	<u>Arrythmia</u>	None	
▶ 16 Mar 2000	Ultrasound	Kidney	28 Apr 2007	None	None	

Clicking this button creates a new table row initially expanded to show an editable details box. Once saved, the row collapses and moves into position based on the current ordering of rows.

						Show all details
						Hide all details
Date	Test	Area	Entered	Diagnoses	Images	
<div style="border: 1px solid #ccc; padding: 10px;"> <p>Test Date <input type="text"/> <input type="text"/> <input type="text"/></p> <p>Test <input type="text"/></p> <p>Other <input type="text"/></p> <p>Area <input type="text"/></p> <p>Images <input type="button" value="Add Image File..."/></p> <p>Comments <input style="width: 100%; height: 40px;" type="text"/></p> <p>Related Diagnoses <input type="text" value="Add a previously entered Diagnosis..."/></p> <p style="text-align: right;"><input type="button" value="Cancel"/> <input type="button" value="Save"/></p> </div>						
▶+ 08 Feb 2001	CT	Head	12 Sep 2007	None	27	
▶+ 08 Feb 2001	EKG	N.A.	24 Jan 2007	<u>Arrythmia</u>	None	
▶ 16 Mar 2000	Ultrasound	Kidney	28 Apr 2007	None	None	

Adding and Removing Related Items

Some data include a number of related items or options (e.g., a Diagnosis may be linked to any number of related Treatments). Users editing this type of data can add or remove options via Add and Remove buttons or menus. The Remove button always appears to the right of the related item, and the Add button or menu always appears at the bottom of the list.



Warning/Error Text

Warning messages directed at the user generally appear as red text in context with the user interface.



Saving Changes

Every editable screen or details box includes a Save button at the lower right; no changes are saved to the database until the user clicks Save.



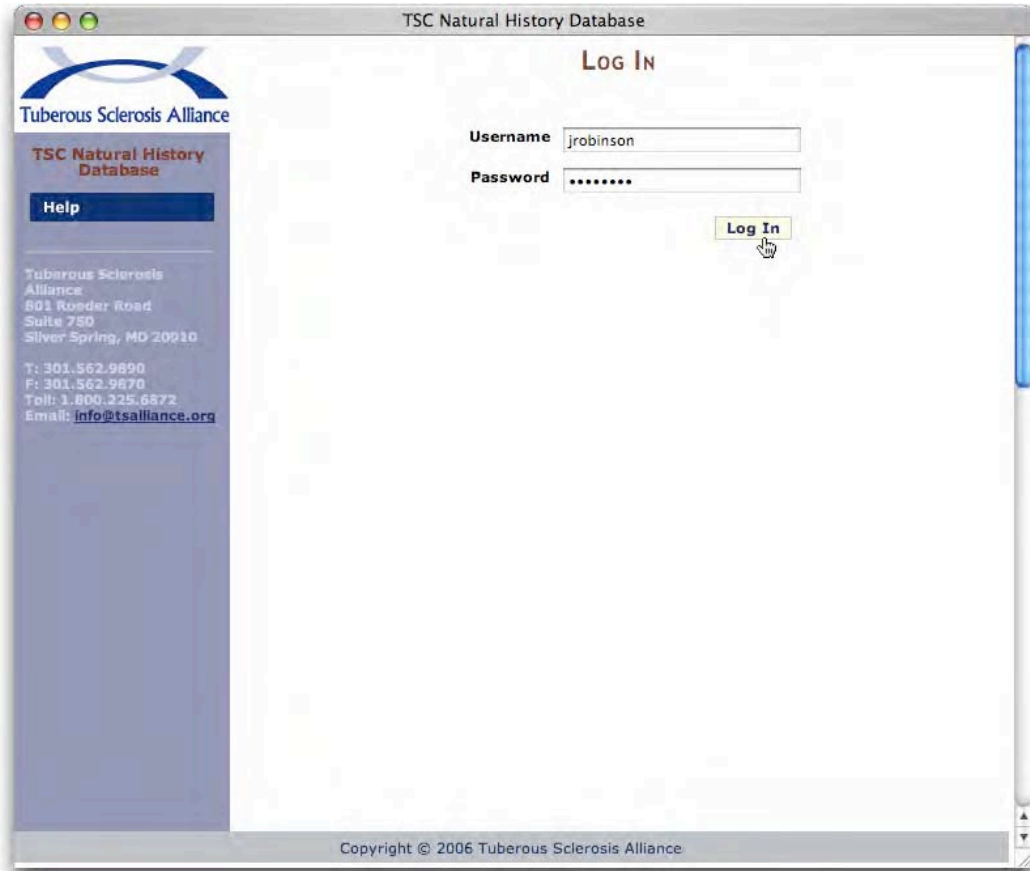
General Rules

- On *Edit* and *Add New* screens, all table rows are collapsed and the expansion triangles should become invisible.
- Users cannot enter future dates on any screen.
- Clicking *Cancel* sends the user to the previous screen, unless otherwise noted.
- Clicking *Save* returns the user to the view-only screen with the newly saved row expanded.
- Upon completing an *Add New* or *Edit* operation, the user is returned to the view-only screen and this screen should remember the user's last-displayed expansion preferences...that is, if certain rows were expanded to show details, these should remain expanded.
- *Delete* buttons require a confirmation dialog: "Are you sure you want to delete this information from database? This operation cannot be undone." Default is *Cancel*. Upon clicking *Delete Information*, user is returned to read-only screen with the deleted row removed.
- The *Administration* button in the sidebar is only visible to clinic and TSA users with *Administer* permissions.
- The *Add New Participant* button in the sidebar and all *Edit*, *Delete*, *Add New*, and *Remove* buttons are not visible to users with *Read-Only* permissions.
- All Participant record tabs are considered incomplete until a user has clicked the *Mark Complete* button, thereby permanently removing the warning text and button.
- *Remove* button behavior: Generally, if a *Remove* button lacks an ellipsis (...), there is no confirmation dialog and the item it refers to disappears immediately. Similarly, when a user adds an item to a list, it appears immediately with a *Remove* button. *Remove...* (with ellipsis) brings up a confirmation dialog.

LOGGING IN

The *Log-In* screen and its associated help screen are the only publicly available screens on the system, accessed by typing the system's URL. To move beyond this screen, all users must enter a valid username and password.

Figure 1: Log-In Screen



Rules

- *Password* field hides entered text.

VIEWING AND ENTERING PARTICIPANT DATA

Participant List

The *Participants* screen appears whenever a user successfully logs into the system. This table shows all Participants to which the current user has access. Generally, when a user at a clinic logs in they see Participants that are or were enrolled at their clinic; TS Alliance administrators will see a list of all Participants in the system.

Figure 2: Participants

Tuberous Sclerosis Alliance

TSC Natural History Database

Hello Janet Robinson

Log Out

List Participants

Add New Participant

Print Form...

Generate Report...

Administration...

Help

Tuberous Sclerosis Alliance
861 Koeder Road
Suite 750
Silver Spring, MD 20910
T: 301.562.9890
F: 301.562.9870
Toll: 1.800.225.8872
Email: info@tsalliance.org

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ID	Age	Sex	Variations	Affected Areas	Clinic	Enrolled	Updated
A12345	30	M	TSC1	Cardiac, Derm, Neuro, Renal	MYO	21 Jun 2006	03 Jul 2006
A23456	29	F	TSC1	Oph	MYO	09 Apr 2006	03 Jan 2007
C34567	45(d)	M	TSC1, 2	Dental, Renal, Oph, Neuro, Psych, Repro, Other	MYO	14 Jun 2008	28 Feb 2010
X09876	10m	M	Unknown	Unknown	MYO	19 Aug 2006	11 Dec 2006
A12345	30	M	TSC1	Cardiac, Derm, Neuro, Renal	MGH	21 Jun 2006	03 Jul 2006
A23456	29	F	TSC2	Oph	MYO	09 Apr 2006	03 Jan 2007
C34567	62(d)	M	TSC1, 2	Dental, Renal, Oph, Neuro	MYO	14 Jun 2008	28 Feb 2010
X09876	10	M	Unknown	Unknown	MYO	19 Aug 2006	11 Dec 2006
A12345	30	M	TSC1	Cardiac, Derm, Neuro, Renal	MYO	21 Jun 2006	03 Jul 2006
A23456	29	F	TSC1	Oph	MYO	09 Apr 2006	03 Jan 2007
C34567	47	M	TSC2	Dental, Renal, Oph, Neuro, Psych, Repro, Other	MYO	14 Jun 2008	28 Feb 2010
X09876	9	M	TSC2	Unknown	MYO	19 Aug 2006	11 Dec 2006
A12345	30	M	TSC1	Cardiac, Derm, Neuro, Renal	MGH	21 Jun 2006	03 Jul 2006
A23456	21	F	TSC1	Oph	MYO	09 Apr 2006	03 Jan 2007

In addition to *ID* number, the table displays other information helpful in identifying a Participant. Users can jump directly to a Participant's record by typing an *ID* number in the *ID*: field; otherwise, users can click on an *ID* (as shown in Figure 2) to view the record.

Every screen in the system includes the navigation bar on the left to provide direct access to major areas from anywhere in the system. For example, users may click the *List Participants* button from anywhere in the system to return to the *Participants* screen.

Searching for Participants

Clicking the Search... link on the *Participants* screen (Figure 2) takes users to a search page where they can specify important matching criteria (Figure 3).

Figure 3: Search



Upon executing a search, users are returned to the *Participants* screen showing only matching Participants in the table. At this time, the original Search... link is replaced with three new options:

- Search These Results... allows the user to perform a new search within the existing results.
- Add Search Results... allows the user to perform an additional search of all Participants and add those results to the existing ones (e.g. add Participants with a different diagnosis).
- Show All restores the original view of Participants, removing all search criteria.

Participant Record

Users access the data for an individual participant via any of the seven “tabs” (*Background, Family, Prenatal, Vitals, Diagnoses, Tests, and Treatments*). These tabs provide both viewing and data entry functions; users with *view/edit* permissions can enter and edit data directly within these tabs.

Background Tab

Clicking an ID number on the *Participant* screen brings up the first of seven tabs under which the Participant’s record is organized. Users who have *view/edit* permissions will see an Edit button at the upper right corner: this button converts the tab from read-only mode (Figure 4) to edit mode (Figure 5). Note that only TS Administrators will see the Verify/Unverify button for consent.

Figure 4: Background Tab (view)

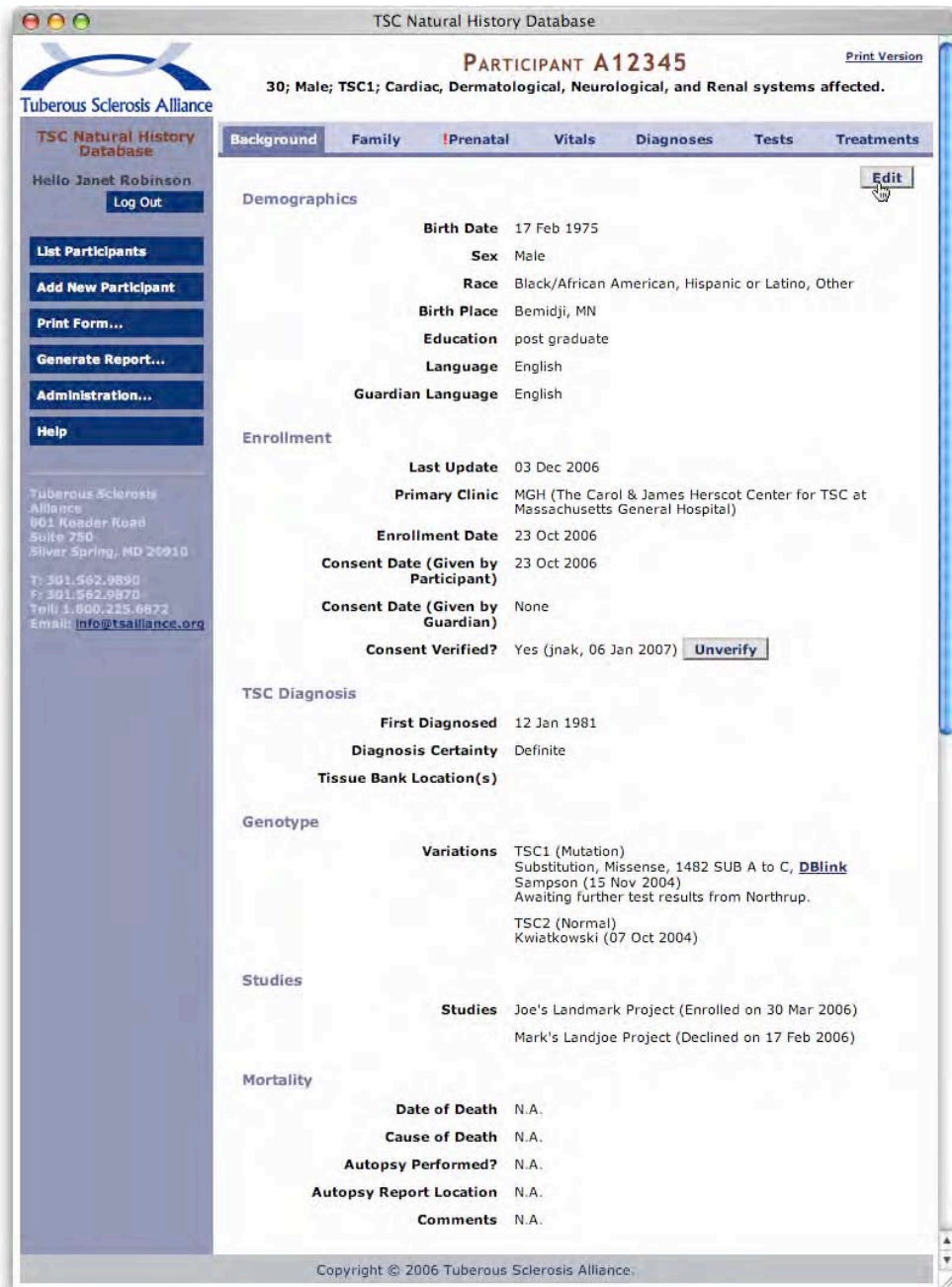


Figure 5: Background Tab (edit)

The screenshot shows the 'Background' tab of the TSC Natural History Database. The interface includes a sidebar with navigation options and contact information, and a main content area with several sections of data entry forms.

TSC Natural History Database
Hello Janet Robinson
Log Out

List Participants
Add Participant
Forms >
Reports >
Administration >
Help

Tuberous Sclerosis Alliance
801 Roeder Road
Suite 750
Silver Spring, MD 20910
T: 301.562.8890
F: 301.562.9878
Tel: 1.800.225.6872
Email: info@tsalliance.org

Background Family Prenatal Vitals Diagnoses Tests Treatments

Demographics

Birth Date: 17 Feb 1975
Sex: Male Female
Race: American Indian/Alaska Native
 Black/African American
 Hispanic or Latino
 Native Hawaiian or other Pacific Islander
 White
 Other
Birth Place: Bemidji, MN
Highest Education Level: Post Graduate
Language: English
Guardian Language: English

Enrollment

Enrollment Date: 23 Oct 2006
Consent Date (Given by Participant): 23 Oct 2006
Consent Date (Given by Guardian): -- -- --

TSC Diagnosis

First Diagnosed: 12 Jan 1981
Diagnosis Certainty: Definite
Tissue Bank Location(s):

Genotype

Variation Gene: TSC1
Variation Type: Mutation
Base Change Type: Substitution
Expression Type: Missense
Desc: 1482 SUB A to C (e.g. 465 SUB T to G)
Database Link: DBlink
Lab: Sampson
Test Date: 15 Nov 2004
Awaiting further test results from Northrup.
Remove

Variation Gene: TSC2
Variation Type: Normal
Base Change Type: --
Expression Type: --
Desc: (e.g. 465 SUB T to G)
Database Link: --
Lab: Kwiatkowski
Test Date: 15 Nov 2004
Remove

Figure 5: Background Tab (edit) *continued*

Variation Gene: TSC2
 Variation Type: Normal
 Base Change Type:
 Expression Type:
 Desc: (e.g. 465 SUB T to G)
 Database Link:
 Lab: Kwiatkowski
 Test Date: 15 Nov 2004

Remove
Add Variation

Studies
 Study associations are maintained by TS Alliance personnel.

Mortality
 Date of Death
 Cause of Death
 Autopsy Performed?
 Autopsy Report Location
 Comments

Cancel Save

Copyright © 2006 Tuberous Sclerosis Alliance.

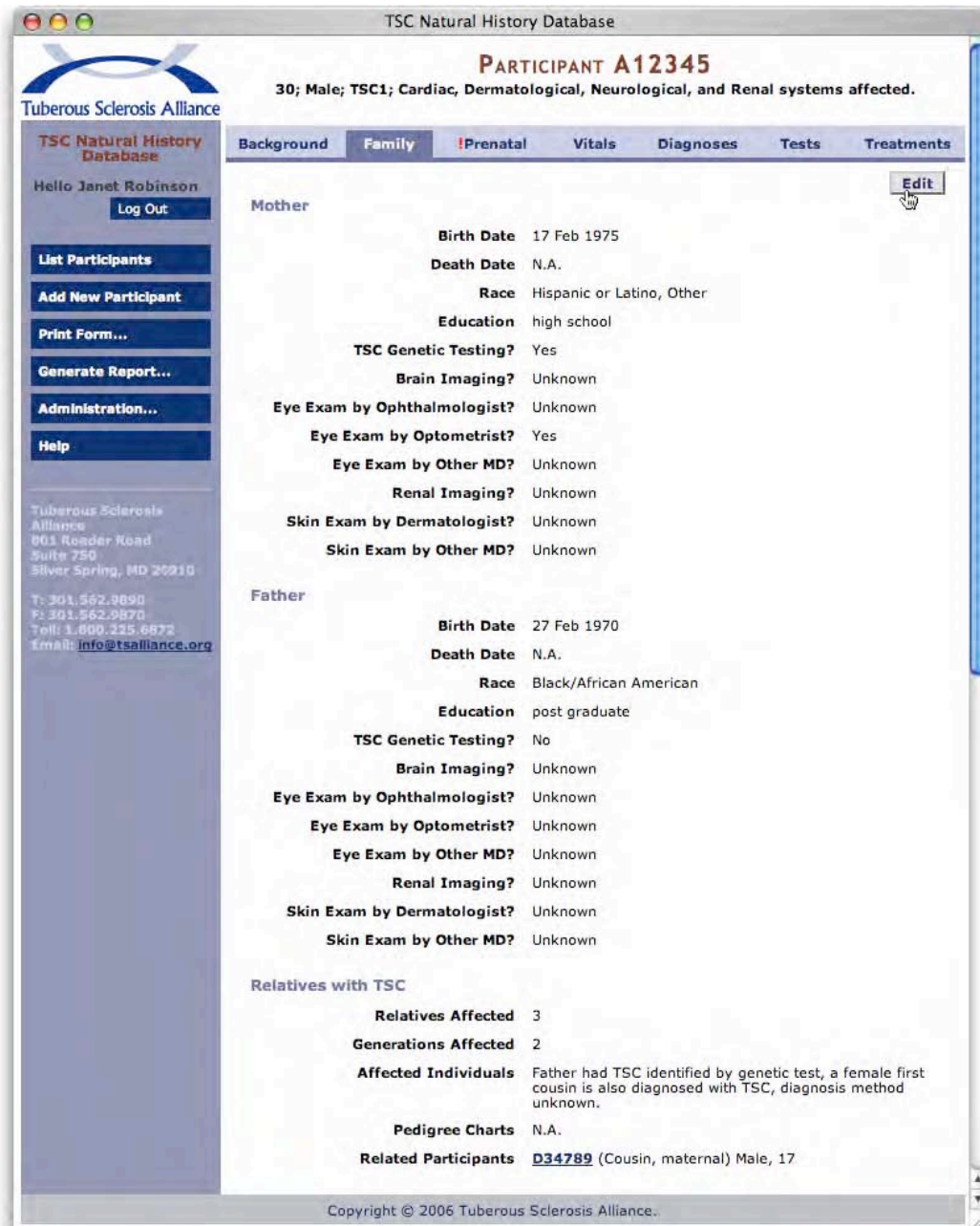
RULES

- In Genotype, *Base Change Type*, *Expression Type*, *Desc*, and *Database Link* fields are disabled whenever *Variation Type* = *Normal*.
- In Genotype, clicking *Remove* causes an immediate screen refresh with the variation removed.
- In Genotype, clicking *Add Variation* causes an immediate screen refresh with a new, unpopulated *Variation* form added to the bottom of the *Variation* list.

Family Tab

The *Family* tab shows information about the Participant’s parents and other relatives, including links to any relatives who are also enrolled in the database. If any pedigree charts have been uploaded to the record, they are also accessible via links from this screen.

Figure 6: Family Tab (view)



RULES

- Clicking a link in Related Participants opens the related Participant’s Background tab in a new browser window.

Figure 7: Family Tab (edit)

TSC Natural History Database

PARTICIPANT A12345
30; Male; TSC1; Cardiac, Dermatological, Neurological, and Renal systems affected.

Background Family **!Prenatal** Vitals Diagnoses Tests Treatments

Mother

Birth Date: 17 Feb 1975
Death Date: -- -- --
Race: American Indian/Alaska Native
 Black/African American
 Hispanic or Latino
 Native Hawaiian or other Pacific Islander
 White
 Other
Highest Education Level: High School
TSC Genetic Testing? Yes
Brain Imaging? --
Eye Exam by Ophthalmologist? --
Eye Exam by Optometrist? Yes
Eye Exam by Other MD? --
Renal Imaging? --
Skin Exam by Dermatologist? --
Skin Exam by Other MD? --

Father

Birth Date: 27 Feb 1970
Death Date: -- -- --
Race: American Indian/Alaska Native
 Black/African American
 Hispanic or Latino
 Native Hawaiian or other Pacific Islander
 White
 Other
Highest Education Level: Post C
TSC Genetic Testing? No
Brain Imaging? --
Eye Exam by Ophthalmologist? --
Eye Exam by Optometrist? --
Eye Exam by Other MD? --
Renal Imaging? --
Skin Exam by Dermatologist? --
Skin Exam by Other MD? --

Birth Date dropdown menu: --, Jan, Feb (selected), Mar, Apr, May, Jun, Jul, Aug, Sep, Oct, Nov, Dec

Tuberous Sclerosis Alliance
TSC Natural History Database
Hello Janet Robinson
Log Out
List Participants
Add New Participant
Print Form...
Generate Report...
Administration...
Help
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F: 301.562.9870
Toll: 1.800.215.6872
Email: info@tsalliance.org

Figure 7: Family Tab (edit) *continued*

The screenshot displays a web-based form titled "Relatives with TSC". It contains several input fields and buttons:

- Affected Relatives:** A text input field containing the number "3".
- Total Siblings (Affected+Unaffected):** A text input field containing the number "3".
- Affected Siblings:** A text input field containing the number "3".
- Affected Generations:** A text input field containing the number "2".
- Affected Individuals:** A text area containing the text: "Father had TSC identified by genetic test, a female first cousin is also diagnosed with TSC, diagnosis method unknown."
- Pedigree Charts:** A button labeled "Choose file...".
- Related Participants:** A section with two rows of controls:
 - Row 1: "Relationship to Participant:" dropdown menu set to "Cousin, maternal", followed by an "ID:" text input field containing "D34789" and a "Remove" button.
 - Row 2: "Relationship to Participant:" dropdown menu set to "Add Relative...", followed by a blank "ID:" text input field.
- At the bottom right, there are "Cancel" and "Save" buttons.
- At the bottom center, a footer reads "Copyright © 2006 Tuberous Sclerosis Alliance."

RULES

- Death Date cannot be prior to Birth Date (may be the same as Birth Date or later).
- *Choose File...* invokes a standard system dialog to select a local file.
- *Remove* causes an immediate screen refresh with the related Participant removed.
- Upon selecting an option from the *Add Relative...* menu, a new blank *ID* field appears below it.

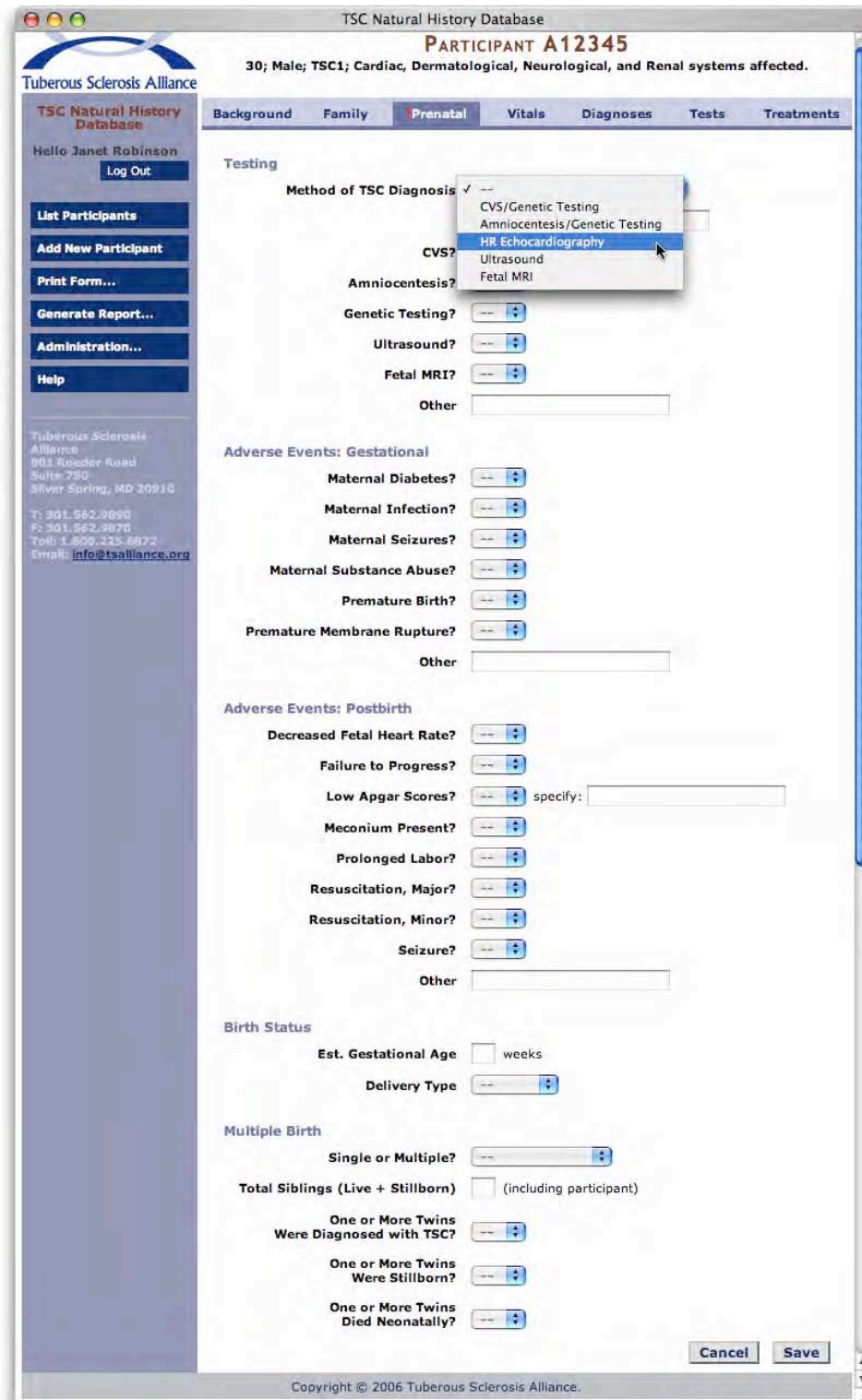
Prenatal Tab

The red exclamation mark on this tab indicates that no one has yet entered prenatal data for this Participant and that no one has marked data entry as "complete" for this area. Hence, all data are "unknown" in Figure 8. Clicking Mark Complete permanently removes the tab marker and warning text at any time, regardless of how much data (if any) has been entered.

Figure 8: Prenatal Tab (view)



Figure 9: Prenatal Tab (edit)



RULES

- All four items following "Single or Multiple?" are disabled unless *Multiple* is selected.

Vitals Tab

Because vital statistics can be measured multiple times, these data are presented in tabular format – a pattern that is repeated for similar reasons in the *Diagnoses*, *Tests*, and *Treatments* tabs. Clicking Edit in a row expands that row into an editable details box, as shown in Figure 11.

Figure 10: Vitals Tab (view)



Figure 11: Vitals Tab (edit)

The screenshot shows a web application window titled "TSC Natural History Database". The main content area displays "PARTICIPANT A12345" with the text "30; Male; TSC1; Cardiac, Dermatological, Neurological, and Renal systems affected." Below this is a navigation menu with tabs: Background, Family, !Prenatal, Vitals (selected), Diagnoses, Tests, and Treatments. The "Vitals" tab contains a table of vitals and an "Add New Vitals" form.

Date	Height	Weight	FOC	BP
26 Jun 2005	140 cm	41 kg	56 cm	120/53 mm Hg
04 May 2003	123 cm	39 kg	42 cm	110/64 mm Hg
12 Aug 2001	101 cm	28 kg	Unknown	102/50 mm Hg

The "Add New Vitals" form includes the following fields:

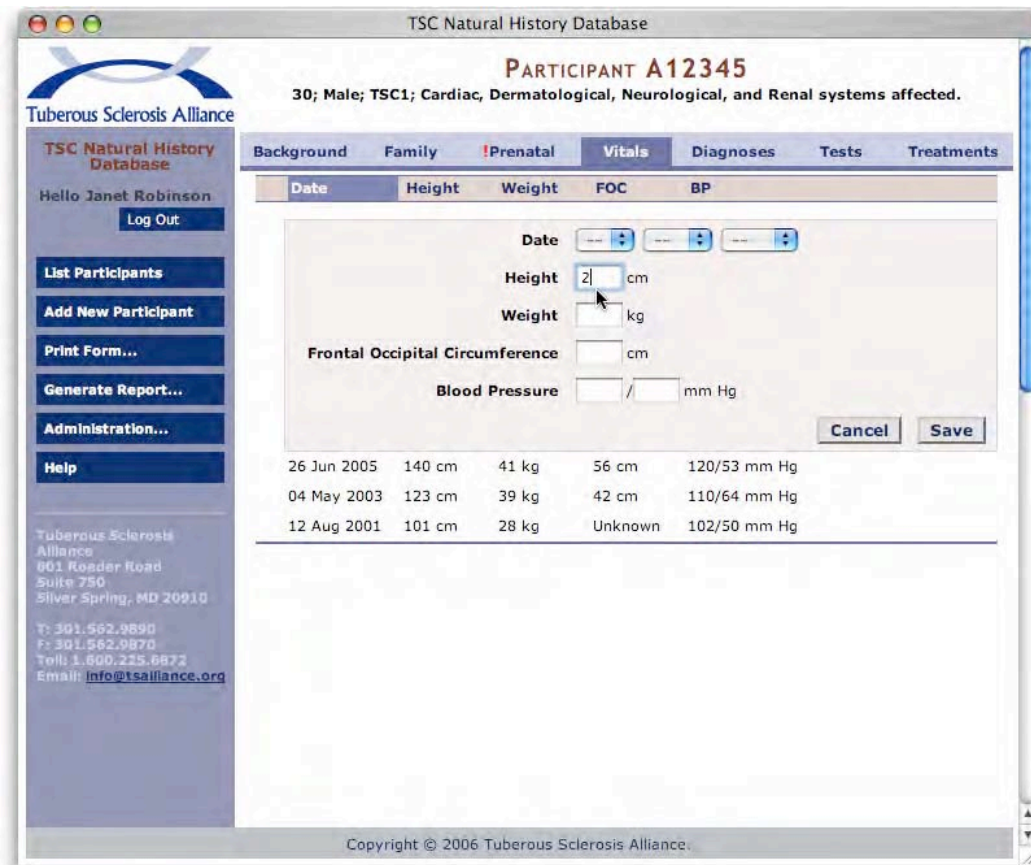
- Date: 04 May 2003
- Height: 123 cm
- Weight: 104 kg
- Frontal Occipital Circumference: 56 cm
- Blood Pressure: 110 / 64 mm Hg

Buttons for "Cancel" and "Save" are located at the bottom right of the form.

Footer: Copyright © 2006 Tuberous Sclerosis Alliance.

Another feature common to screens with tabular data is the Add New button near the upper left, which adds a new empty row – expanded for data entry – to the table (Figure 12).

Figure 12: Vitals Tab (add new)



Diagnoses Tab

As with Vitals, Diagnoses appear in tabular format, with each row representing a single diagnosis for the Participant. In Figure 13, the user has chosen to view the details of a rhabdomyoma diagnosis that was made on July 30, 1994. Clicking Edit converts the details box to edit mode (Figure 14).

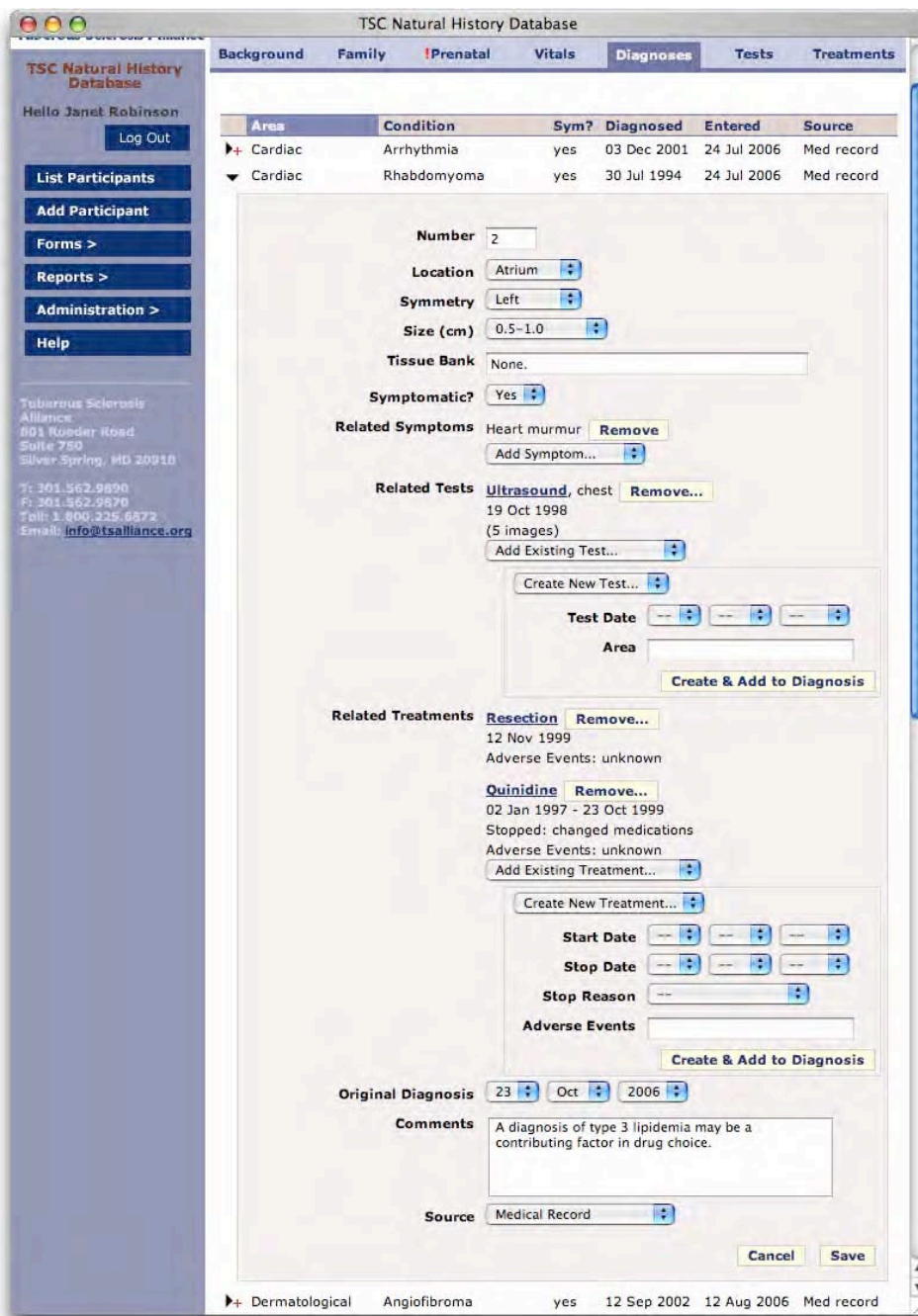
Figure 13: Diagnoses Tab (view)



RULES

- Links to related Tests and Treatments send users to Tests or Treatments tab, with the appropriate row expanded and at the top of the screen.

Figure 14: Diagnoses Tab (edit)



RULES

- Selecting from an *Add Existing* menu immediately places the selection on the screen.
- Clicking *Remove...* (for Related Tests and Related Treatments only) brings up a dialog: "You may unlink the Test/Treatment from this Diagnosis while retaining the Test/Treatment in the database, or you may delete the Test/Treatment from the database." Options: "Remove Link Only" / "Remove Link and Delete" / "Cancel".
- For Related Symptoms, *Remove* immediately removes the symptom from the screen.

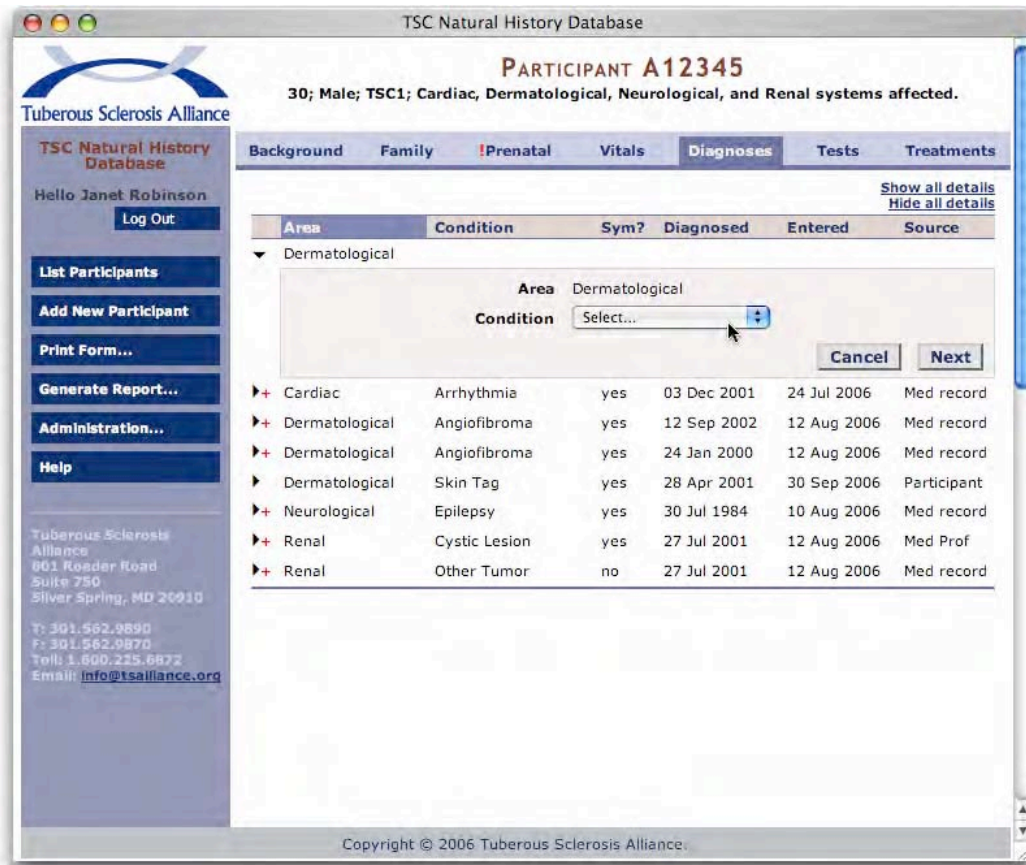
Clicking Add New Diagnosis creates a new empty row in the table. Because of the complexity of Diagnosis data, there is a stepwise process for creating a new Diagnosis. In the first step, users must select an organ system category, or Area (Figure 15).

Figure 15: Diagnoses Tab (add new, step 1)



Clicking Next adds a prompt to select a *Condition* that is valid for the chosen *Area* (Figure 16). The Conditions available in this menu depend on the Conditions dictionary (see *Conditions Dictionary* in the *Administration* section later in this chapter).

Figure 16: Diagnoses Tab (add new, step 2)



RULES

- *Condition* menu contains only those conditions within the selected *Area*.

Upon choosing a *Condition* (*Confetti Lesion* in this example), a standard edit-mode details box appears. The precise fields that appear on this screen depend on what fields have been set up for the given Condition (see *Conditions Dictionary* in the *Administration* section later in this chapter).

Figure 17: Diagnoses Tab (add new, step 3)

The screenshot shows the 'Diagnoses' tab in the TSC Natural History Database. The main form is for adding a new diagnosis for 'Confetti Lesion' in the 'Dermatological' area. The form includes several sections:

- Symmetry:** Unknown (dropdown)
- Location:** Unknown (dropdown)
- Symptomatic?:** -- (dropdown)
- Related Symptoms:** Add Symptom... (dropdown)
- Related Tests:** Add Existing Test... (dropdown)
- Test Section:** Create a New Test... (dropdown), Test Date (date picker), Area (text input), Create & Add to Diagnosis (button)
- Related Treatments:** Add Existing Treatment... (dropdown)
- Treatment Section:** Create New Treatment... (dropdown), Start Date (date picker), Stop Date (date picker), Stop Reason (dropdown), Adverse Events (text input), Create & Add to Diagnosis (button)
- Original Diagnosis:** -- (dropdown)
- Comments:** Text area
- Source:** Unknown (dropdown)

At the bottom, a table shows the current state of the diagnosis:

Area	Condition	Sym?	Diagnosed	Entered	Source
Cardiac	Arrhythmia	yes	03 Dec 2001	24 Jul 2006	Med record

RULES

- Related Symptoms *Add Symptom...* menu is disabled when users sets Symptomatic? to *No*.

Clicking Save completes the process and the system automatically relocates the new table row based on the current ordering criteria (in this case, it's alphabetical by *Area*).

About Tests and Treatments

A given Diagnosis can be linked to any number of Tests and Treatments. These Tests and Treatments are not actually part of the Diagnosis, but are shown as linked items that can be viewed from, added to, or removed from the Diagnosis.

For example, the *Rhabdomyoma* Diagnosis shown in Figure 14 is linked to one Test (an *Ultrasound*) and two Treatments (*Resection* and *Quinidine*). The Remove... buttons would provide the option of either simply unlinking the Test/Treatment from the Diagnosis OR deleting the Test/Treatment from the Participant's record. Therefore, Tests and Treatments can exist on their own, without any links to a Diagnosis. All Tests and Treatments — regardless of linkage — are entered, viewed, and edited from their respective tabs.

Note that the Add a previously entered Test/Treatment menus appearing on the Diagnosis screen contain the Tests and Treatments that have already been entered for the Participant in the *Tests* and *Treatments* tabs. This means, naturally, that a user must first create a Test or Treatment before linking it to a Diagnosis.

Tests Tab

The Tests tab provides a table of all diagnostic Tests that the Participant has received (Figure 18). Where tests have contributed to a Diagnosis, the table also provides a link to that Diagnosis. A Test may also include any number of images; clicking on an image file name or thumbnail opens the full-sized image in a new browser window. In edit mode (Figure 19), users can add and remove links to Diagnoses (the same operation can also be performed from the Diagnoses in the *Diagnoses* tab).

Figure 18: Tests Tab (view)



RULES

- Clicking a link in the Diagnoses column of the table takes user to the top of an expanded row in the Diagnoses tab.
- Clicking thumbnail or file name opens full-size image in a new window.

Figure 19: Tests Tab (edit)

TSC Natural History Database

PARTICIPANT A12345

30; Male; TSC1; Cardiac, Dermatological, Neurological, and Renal systems affected.

Tuberous Sclerosis Alliance

TSC Natural History Database

Hello Janet Robinson

[Log Out](#)

[List Participants](#)

[Add New Participant](#)

[Print Form...](#)

[Generate Report...](#)

[Administration...](#)

[Help](#)

Tuberous Sclerosis Alliance
 8611 Rosier Road
 Suite 750
 Silver Spring, MD 20910
 T: 301.562.9890
 F: 301.562.9870
 Toll: 1.800.225.6872
 Email: info@tsalliance.org

Background
Family
!Prenatal
Vitals
Diagnoses
Tests
Treatments

[Add New Test](#)
[Show all details](#)
[Hide all details](#)

Data	Test	Area	Entered	Diagnoses	Images
▶ 08 Feb 2001	CT	Head	12 Sep 2007	None	27
▶ 08 Feb 2001	EKG		24 Jan 2007	Arrythmia	None
▶ 16 Mar 2000	Ultrasound	Kidney	28 Apr 2007	None	None
▶ 09 Dec 1998	X-ray	Chest	30 Jul 2006	None	3
▼ 19 Oct 1998	Ultrasound	Chest	10 Aug 2006	Rhabdomyoma Cystic Lesion	5

Test Date 19 Oct 1998

Test Ultrasound

Area

Images

[Ultrasound_Heart.jpg \(1.3 MB\)](#) [Remove...](#)

Enormous State University has poor imaging facilities.

[Echo.jpg \(1.3 MB\)](#) [Remove...](#)

This one is better. The full study contains 67 more images gathered over the course of 17 months, before and after surgical resection. A very complete study.

[Ultrasound_Heart_Quad.gif \(0.04 MB\)](#) [Remove...](#)

I don't think this one is useful.

[Add Image File...](#)

Comments

Related Diagnoses

[Rhabdomyoma](#) 30 Jul 1984 [Remove...](#)

[Cystic Lesion](#) 07 Feb 1989 [Remove...](#)

[Cancel](#) [Save](#)

▶ 17 Apr 1997	X-ray	Head	10 Aug 2006	None	None
▶ 24 Sep 1996	X-ray	Chest	10 Aug 2006	None	None

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When editing a test (or entering a new test as shown in Figure 20), users may add or remove any number of images and provide text comments for each. When uploading a new image (by clicking the Add Image File... button), users will be prompted by their system software to select a file from their hard drive or network. Once added, the new image thumbnail appears in the details box. Users may add additional images, and when finished they must click Save to confirm the addition(s).

Figure 20: Tests Tab (add new)

TSC Natural History Database

PARTICIPANT A12345
30; Male; TSC1; Cardiac, Dermatological, Neurological, and Renal systems affected.

Background Family **!Prenatal** Vitals Diagnoses **Tests** Treatments

Show all details
Hide all details

Date	Test	Area	Entered	Diagnoses	Images
▶ + 08 Feb 2001	CT	Head	12 Sep 2007	None	27
▶ + 08 Feb 2001	EKG	N.A.	24 Jan 2007	Arrythmia	None
▶ 16 Mar 2000	Ultrasound	Kidney	28 Apr 2007	None	None
▶ + 09 Dec 1998	X-ray	Chest	30 Jul 2006	None	3
▶ 19 Oct 1998	Ultrasound	Chest	10 Aug 2006	Rhabdomyoma Cystic Lesion	5
▶ 17 Apr 1997	X-ray	Head	10 Aug 2006	None	None
▶ 24 Sep 1996	X-ray	Chest	10 Aug 2006	None	None

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Treatments Tab

Like the *Tests* tab, this area displays a table of Treatments the Participant has received, along with any linked Diagnoses. Because Treatments are often given in response to a Diagnosis, unlinked Treatments should be rare. As shown by the sample data in Figure 21, all but the *Clozapine* Treatment show at least one linked Diagnosis.

Figure 21: Treatments Tab (view)

TSC Natural History Database

PARTICIPANT A12345
30; Male; TSC1; Cardiac, Dermatological, Neurological, and Renal systems affected.

Background Family **Prenatal** Vitals Diagnoses Tests **Treatments**

[Add New Treatment](#) [Show all details](#)
[Hide all details](#)

Start	Stop	Treatment	Entered	Diagnoses
▶+ 12 Feb 2006	12 Feb 2006	Excision	14 Mar 2006	Tumor
▶+ 31 Jan 2006	31 Jan 2006	Resection-left	14 Mar 2006	Cystic Lesion
▶+ 22 Apr 2005	Current	Clozapine	23 May 2006	None
▶+ 22 Apr 2005	15 Jan 2006	Lithium	22 Jun 2006	Acute Stress Disorder
▼ 02 Jan 1997	23 Oct 1999	Quinidine	10 Aug 2006	Rhabdomyoma

[Delete](#) [Edit](#)

Treatment Quinidine

Start Date 02 Jan 1997

Stop Date 23 Oct 1999

Stop Reason changed medications

Adverse Events Unknown

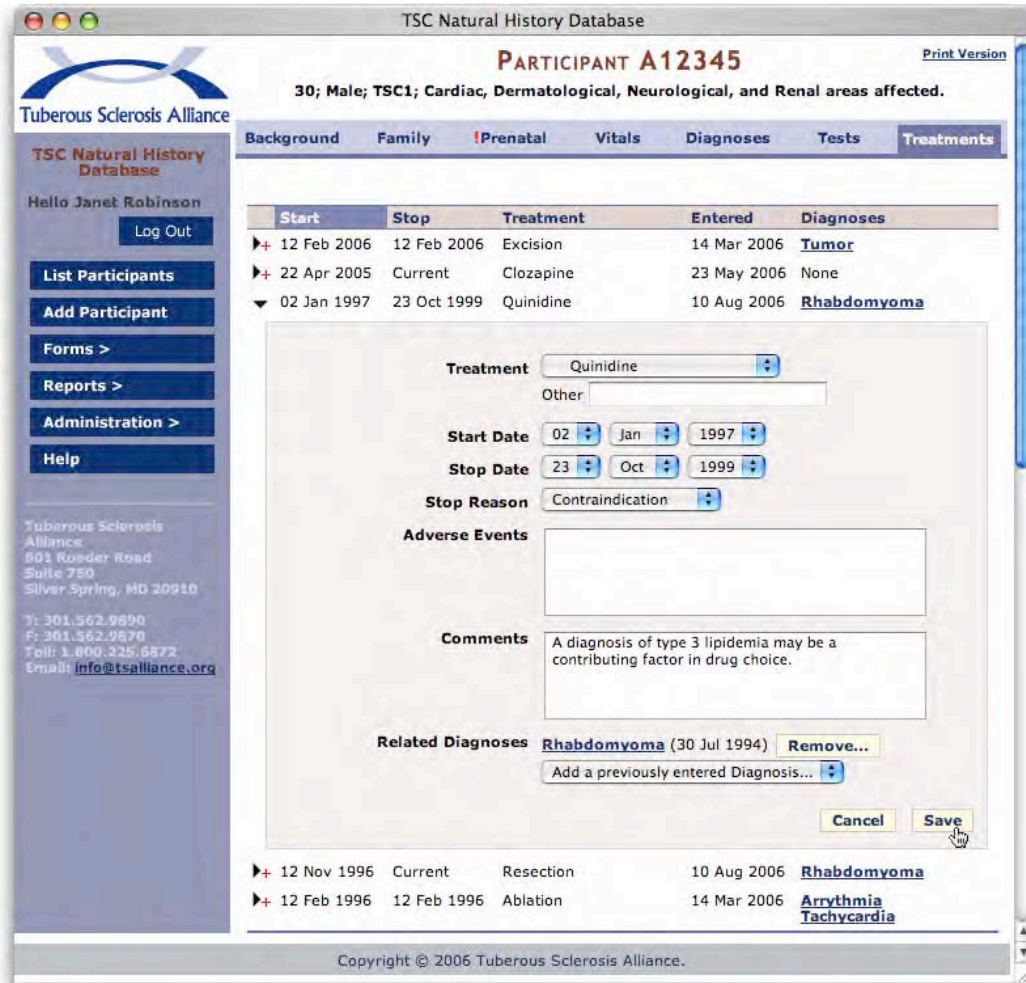
Comments A diagnosis of type 3 lipidemia may be a contributing factor in drug choice.

Related Diagnoses [Rhabdomyoma](#) (30 Jul 1994)

▶+ 12 Nov 1996	Current	Resection	10 Aug 2006	Rhabdomyoma
▶+ 12 Feb 1996	12 Feb 1996	Ablation	14 Mar 2006	Arrythmia Tachycardia

Copyright © 2006 Tuberous Sclerosis Alliance.

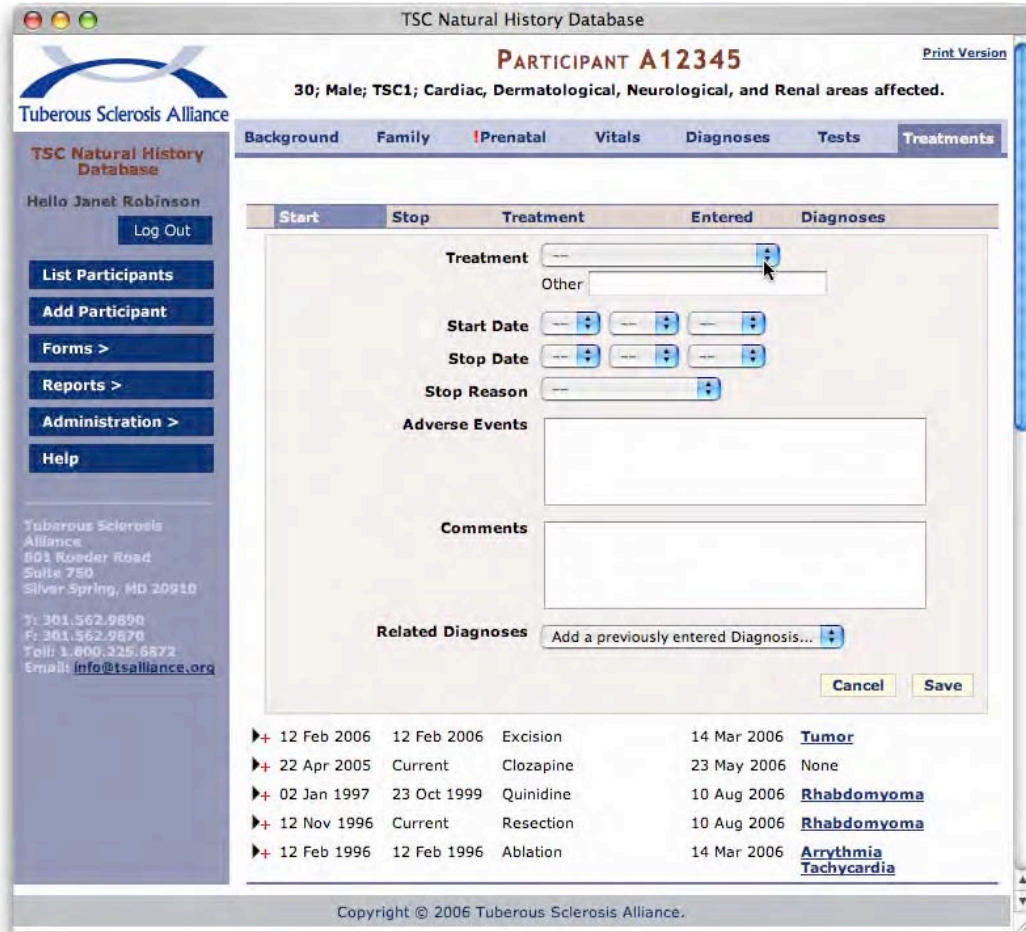
Figure 22: Treatments Tab (edit)



RULES

- The Stop Date must be the same as or later than the Start Date.

Figure 23: Treatments Tab (add new)



CREATING NEW PARTICIPANTS

Creating a new Participant requires entering a gender and birth date. Then, the system automatically assigns an ID and a new set of empty tabs becomes available for data entry, viewing, and editing.

Users with edit permissions can click the Add New Participant button on the left-hand menu bar to create a new Participant record (Figure 24). The current user's clinic is automatically assigned as the new Participant's Primary Clinic (Figure 25).

Figure 24: Add Participant (step 1)

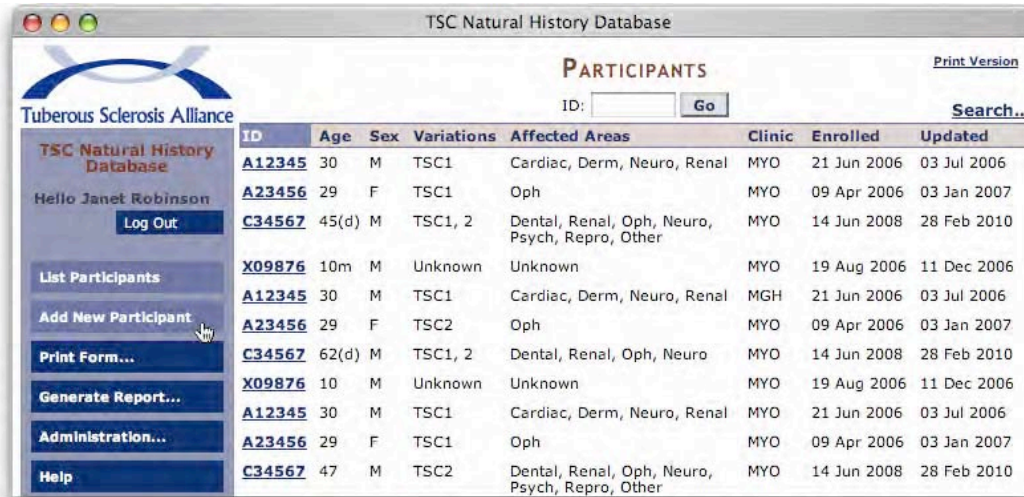
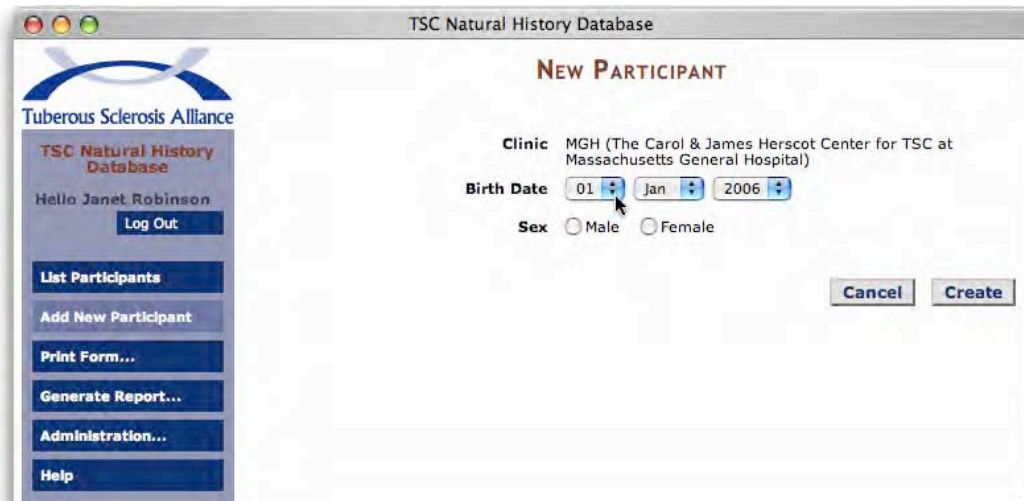


Figure 25: Add Participant (step 2)

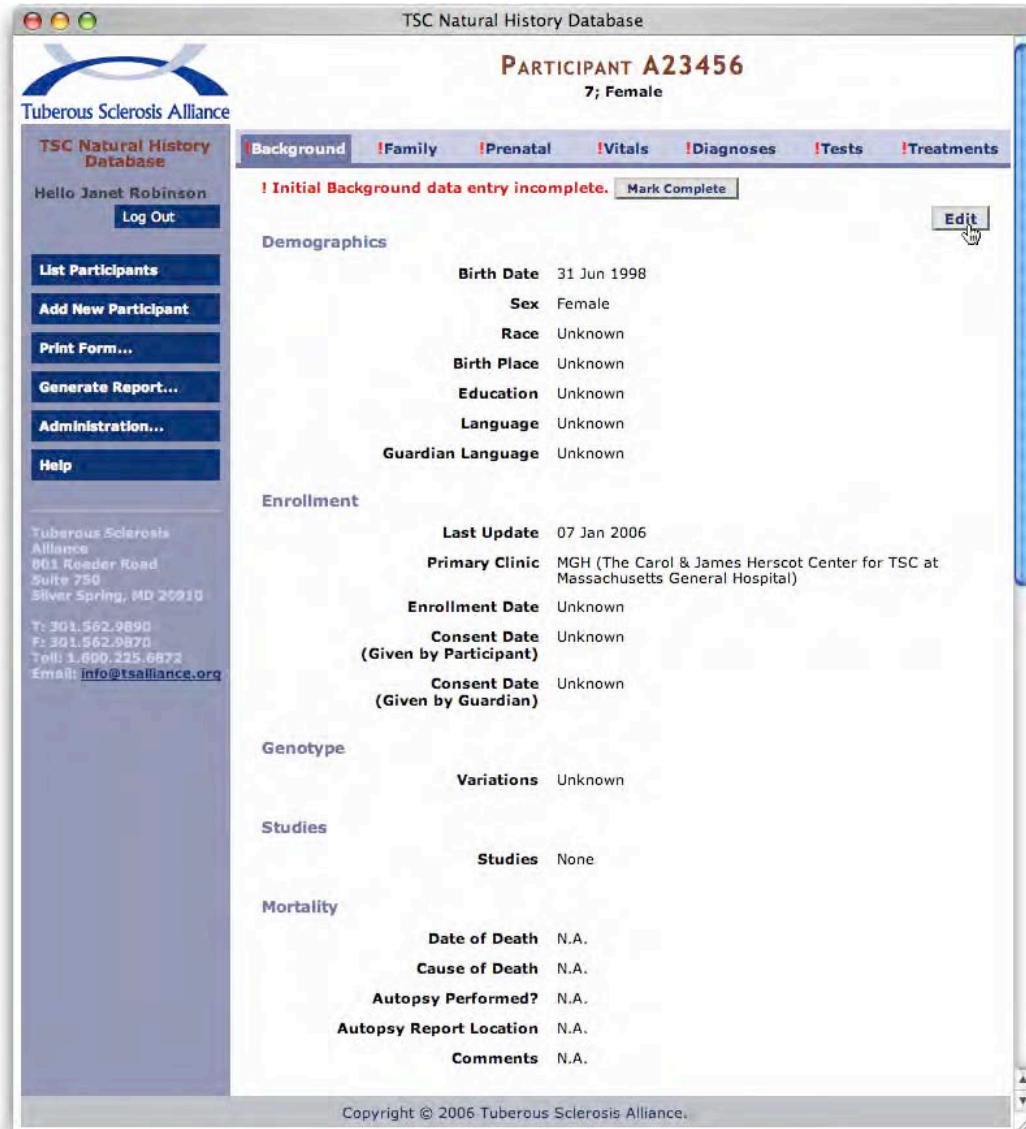


RULES

- Birth Date and Sex are required fields.
- Create button sends user to the Background tab for the new Participant.

Clicking Create in Figure 25 opens the first tab (*Background*) in the new Participant's record (Figure 26). Each tab is initially marked incomplete; users may (at their own discretion) click the Mark Complete buttons to remove the reminders as they complete each tab.

Figure 26: Empty Record for New Participant



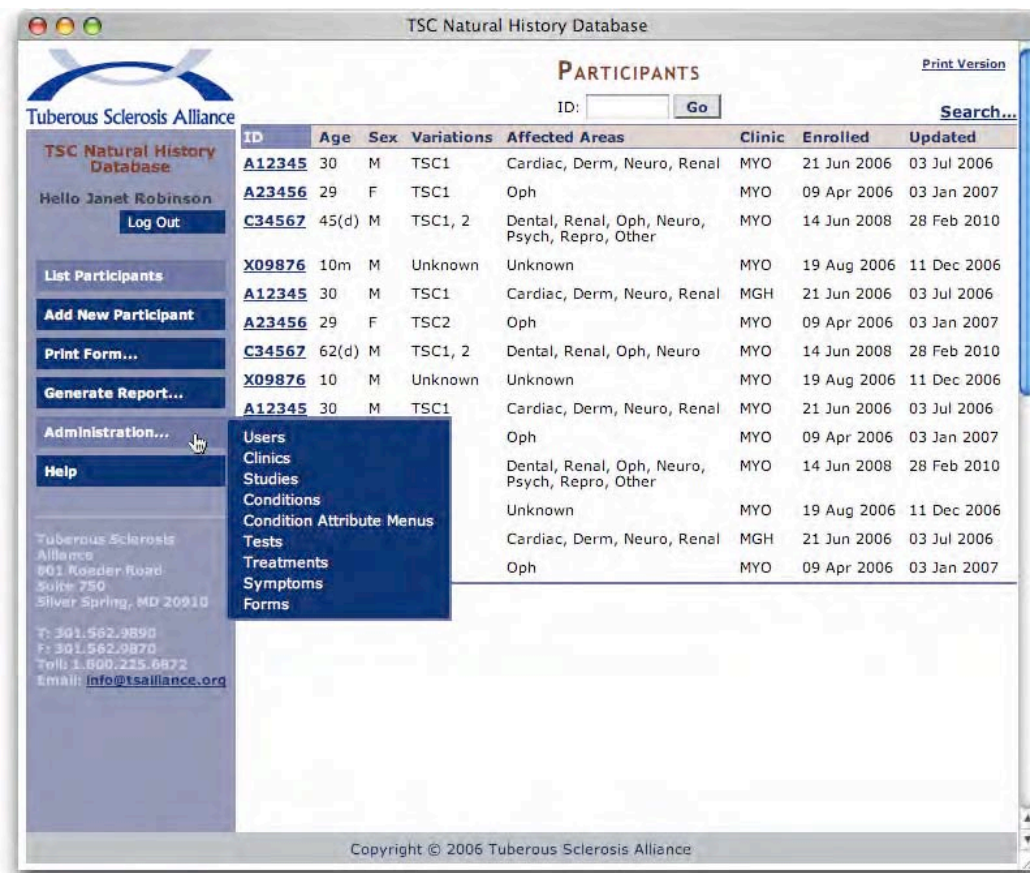
ADMINISTRATION

Access

Those with administrative permissions can manage users, clinics, studies, data collection forms, and the various medical dictionaries that define much of the data entry system. Administrative functions are accessed from any screen via the *Administration...* popup menu on the sidebar as shown in Figure 27.

With the single exception of the *Users* screen, only TS Alliance administrators have access to administration screens. Local clinic administrators can access the *Users* screen to create nonadministrative users. The *Administration...* menu is not visible to nonadministrative users.

Figure 27: Access to Administration Screens



RULES

- A clinic user with *Administer* permissions only sees the *Users* option in the *Administration* menu.

Users

Database users can be added, modified, and deleted from the *Users* screen (Figure 28). An administrator’s ability to perform certain operations depends on their permissions level, *i.e.* a clinic-level administrator cannot create or modify other clinic administrators or TS Alliance administrators. The user table shows all users to which the administrator has access. The expansion triangle for each user displays a details box from which one can delete or edit a user—note that details boxes on administration screens work identically to those appearing on the Participant record screens.

Figure 28: Users (view)

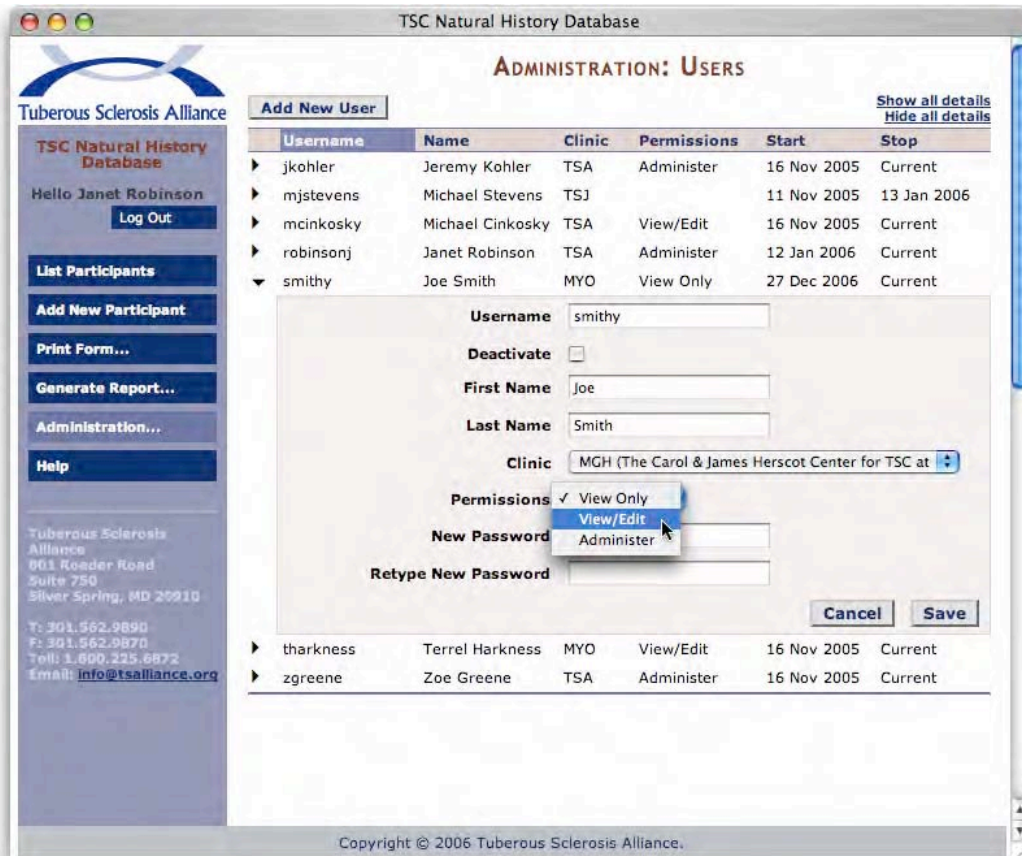


In edit mode (Figure 29) users can be deactivated, thus removing all access permissions. When a user is deactivated, they remain in the user table with a *Stop* date. If the user is later reactivated, the *Stop* date becomes *Current*.

Three permissions levels are available to TS Alliance administrators; local clinic administrators can only set permissions to *View-Only* or *View/Edit* (and they can only see users who are at their clinic).

For local Clinic administrators, their own clinic is automatically assigned to any users they create. TS Alliance administrators may assign users to any Clinic; to create another TS Alliance administrator, they would set the user's Clinic to *TS Alliance*.

Figure 29: Users (edit)



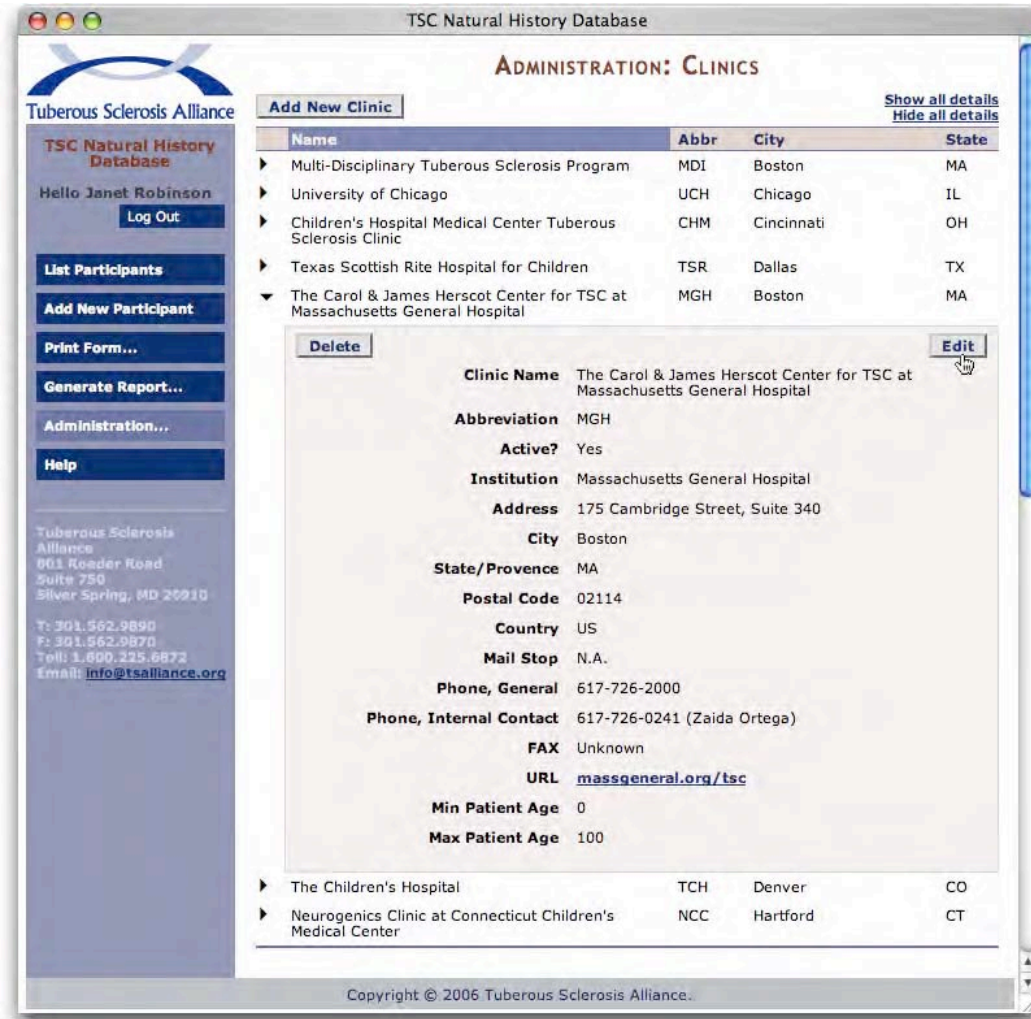
RULES

- Clinic users do not see the *Administer* option.
- Clinic users do not see *TS Alliance* in the Clinic menu.

Clinics

TS Alliance administrators use the *Clinics* screen (Figure 30) to set up Clinics so that they can be assigned to users and to Participants. This screen also tracks general and contact information about each Clinic.

Figure 30: Clinics (view)

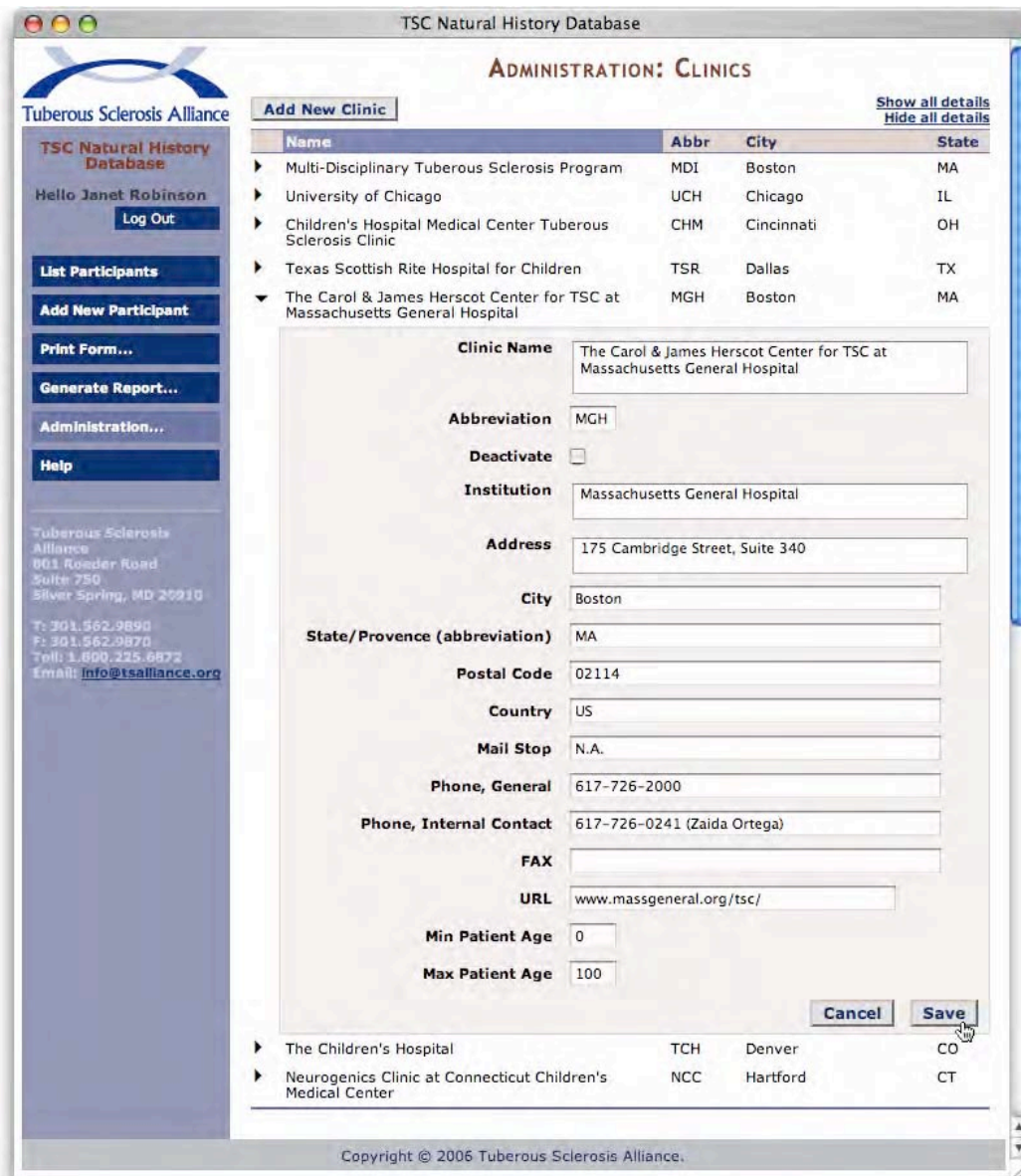


RULES

- The URL link opens in a new browser window.

When editing a Clinic, administrators can deactivate it. This preserves the Clinic information, but renders it unassignable to users and Participants.

Figure 31: Clinics (edit)



RULES

- The Abbreviation is always 3 uppercase alpha characters.

Studies

Studies must be entered into the system before they can be associated with a Participant's record. Studies requiring an approval process may have their approval status tracked on this screen (see Figure 33).

Figure 32: Studies (view)

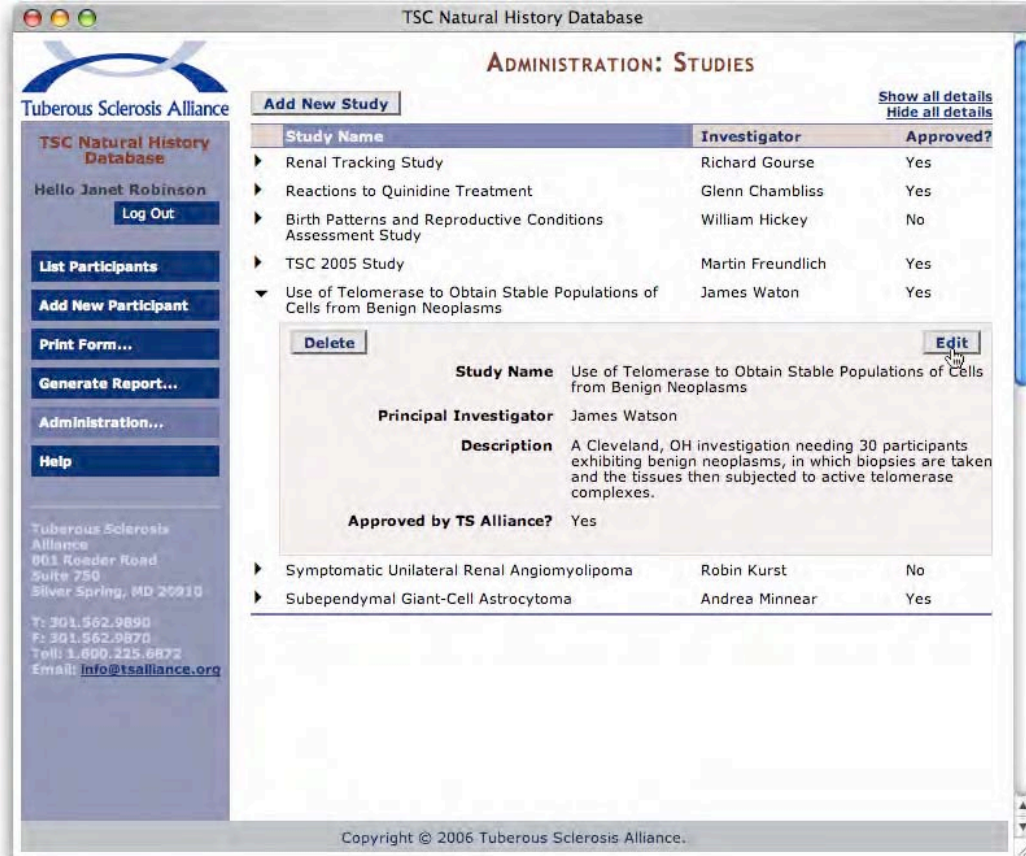
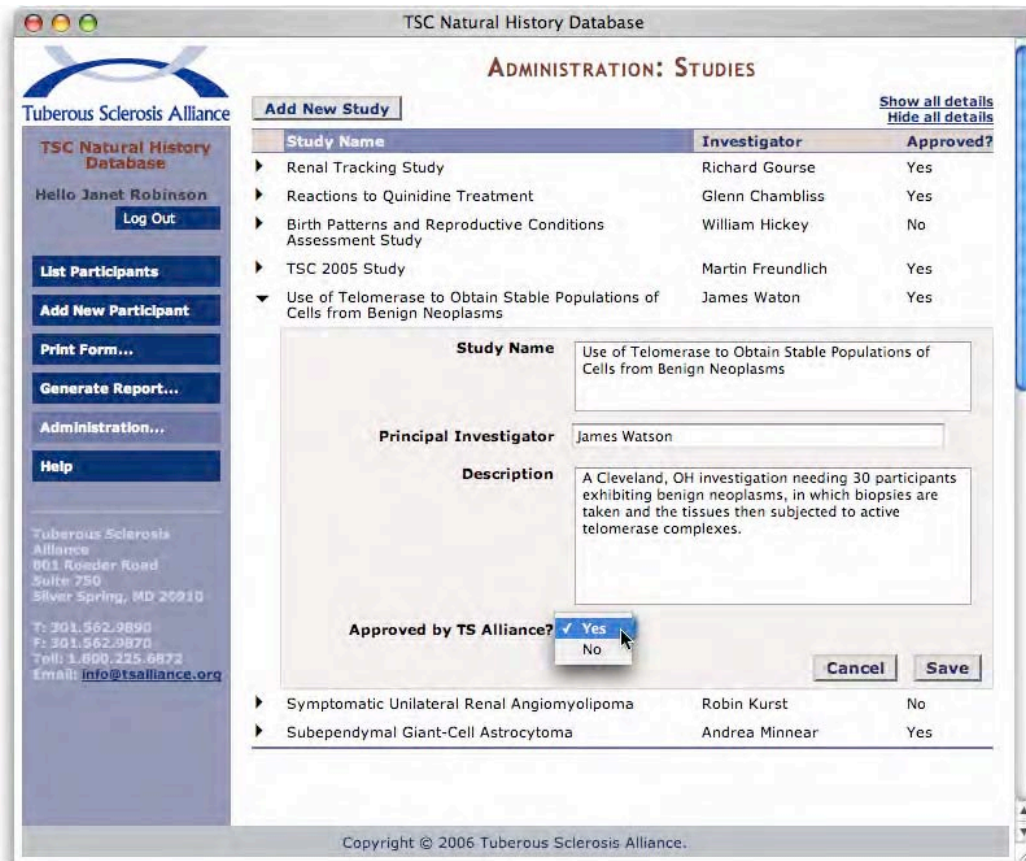


Figure 33: Studies (edit)



Conditions

The most complex operation for TS Alliance administrators is setting up a new Condition. The system maintains a "dictionary" of Conditions (with Attributes) so that users may include them in Diagnoses. Conditions are configured on the *Conditions* screen (Figure 34).

In the Conditions table, the numbers in the *Symp.*, *Tests*, and *Treat.* columns indicate how many defined Symptoms, Tests, and Treatments the Condition is configured to "ask for" when being included in a Participant's Diagnosis. Zero in these columns indicates that a Condition asks for the information, but does not supply a list of options; *No* means the Condition is set to *Don't Ask*.

The *?Sym* column indicates whether the Condition will ask if it is symptomatic.

The *More Attributes* column lists additional custom attributes (e.g. sizes, locations, etc.) it should ask for, if any.

In examples earlier in this section, the Participant's *Diagnoses* tab showed a Diagnosis of *Rhabdomyoma*; here we show what *Rhabdomyoma* looks like in the Conditions dictionary. It is this dictionary entry that determines exactly what fields appear in the *Diagnosis* tab.

The conditions table lists all conditions currently in the dictionary. In edit mode (Figure 35), administrators can modify all of the information, including adding, removing, and configuring attributes.

Figure 34: Conditions (view)

TSC Natural History Database

ADMINISTRATION: CONDITIONS

[Add New Condition](#)
[Show all details](#)
[Hide all details](#)

Area	Name	?Sym.	Symp.	Tests	Treat.	More Attributes
▶ Cardiac	Arrhythmia	Yes	7	3	3	
▶ Cardiac	Coarctation of Aorta	Yes	2	3	1	
▼ Cardiac	Rhabdomyoma	Yes	2	3	No	Number, Symmetry, Location, Size, Bank

[Delete](#)
[Edit](#)

Area Cardiac

Name Rhabdomyoma

Description Benign tumor of striated muscle.

Symptom Options Do ask if symptomatic
Do ask for Symptoms:
Cardiomegaly
Heart Failure

Test Options Do ask for Tests:
CT
Echocardiogram
MRI

Treatment Options Don't ask for Treatments

More Attributes

Attribute Name	Number
Description	How many exist?
Required	No
Data Type	Integer
Attribute Name	Symmetry
Description	Left, right, or bilateral
Required	No
Data Type	Menu: symmetry
Attribute Name	Location
Description	Area of the heart
Required	No
Data Type	Menu: Heart Area
Attribute Name	Size (cm)
Description	
Required	No
Data Type	Menu: Size (small)
Attribute Name	Bank
Description	Where has related tissue been banked?
Required	No
Data Type	Text
Character Length	250

▶ Cardiac	Tachycardia	Yes	6	3	3	
▶ Cardiac	Other	Yes	7	3	3	
▶ Dental	Cavities	No	No	No	No	
▶ Dental	Gingival Fibroma	Yes	No	No	1	Number
▶ Dental	Gingival Hyperplasia	Yes	No	No	1	

Figure 35: Conditions (edit)

TSC Natural History Database

Log Out

▼ Cardiac Rhabdomyoma Yes 2 3 No Number, Symmetry, Location, Size, Bank

Area Cardiac

Name Rhabdomyoma

Description Benign tumor of striated muscle.

Symptom Options

- Ask if symptomatic
- Ask for Symptoms
 - Cardiomegaly Remove...
 - Heart failure Remove...
 - Add Symptom...

Test Options

- Ask for Tests
 - CT Remove...
 - Echocardiogram Remove...
 - MRI Remove...
 - Add Test...

Treatment Options

- Ask for Treatments
 - Add Treatment...

More Attributes

Attribute Name Number

Description How many exist?

Required

Data Type Integer Remove Attribute...

Attribute Name Symmetry

Description Left, right, or bilateral

Required

Data Type Menu: Symmetry Remove Attribute...

Attribute Name Location

Description Area of the heart

Required

Data Type Menu: Heart Area Remove Attribute...

Attribute Name Size (cm)

Description

Required

Data Type Menu: Size (small) Remove Attribute...

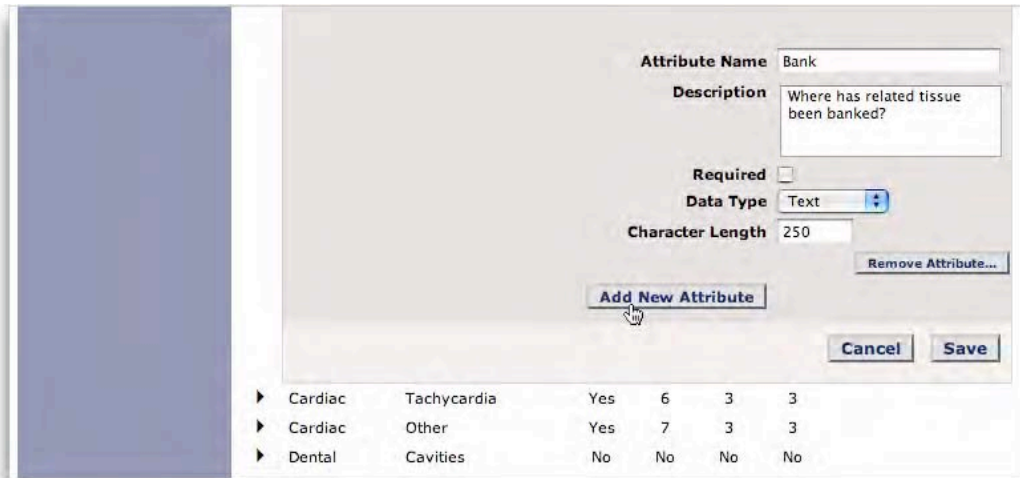
Left Sidebar:

- List Participants
- Add New Participant
- Print Form...
- Generate Report...
- Administration...
- Help

Contact Information:

Tuberous Sclerosis Alliance
 601 Rosser Road
 Suite 750
 Silver Spring, MD 20910
 T: 301.562.9890
 F: 301.562.9870
 Toll: 1.800.325.6872
 Email: info@tsalliance.org

Figure 35: Conditions (edit) *continued*



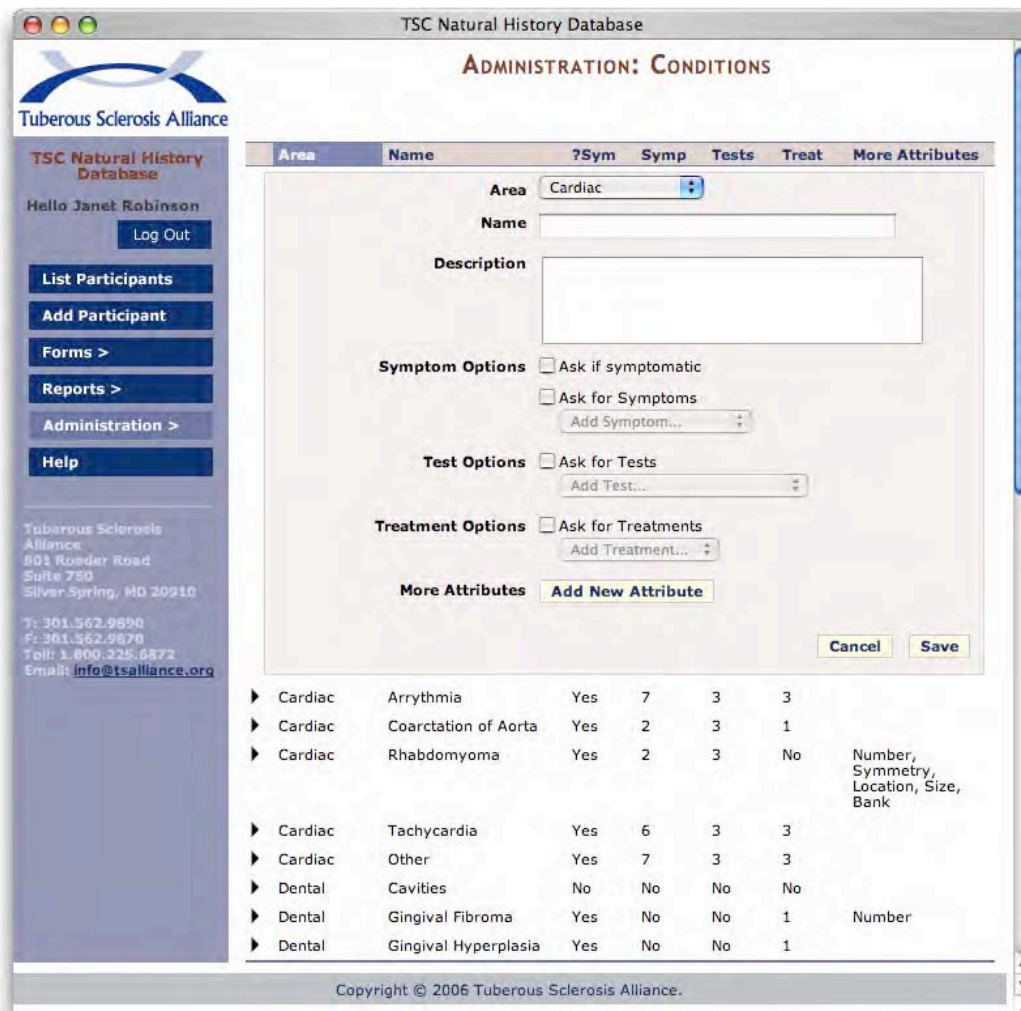
RULES

- *Name* menu shows conditions only for the selected *Area*.
- The select menu following an *Ask For* checkbox is disabled when the checkbox is unchecked.

A Condition may include any number of custom attributes in the *More Attributes* area (*Number, Symmetry, Location, Size, and Bank* in this example). Each attribute is fully configurable with various options depending on what *Data Type* is selected. (If the data type is a menu of options, these menus are set up on the *Condition Attribute Menus* screens as shown in Figures 37 - 39). Many Conditions will have no custom attributes.

Clicking Add New Condition creates a new expanded row in the table (Figure 36), where a condition can be named; configured to ask for symptoms, tests, and treatments; and populated with custom attributes.

Figure 36: Conditions (add)



RULES

- Add menus are disabled unless their Ask For checkboxes are checked.

Condition Attribute Menus

One of the custom attributes in the example shown in Figure 35 is *Size (cm)*, and it is set to display a menu called "Size (small)." This menu was previously set up on the *Condition Attribute Menu* screen, accessible by selecting the *Condition Attribute Menus* link on the Administration... popup menu (Figure 37).

Figure 37: Condition Attribute Menus Access



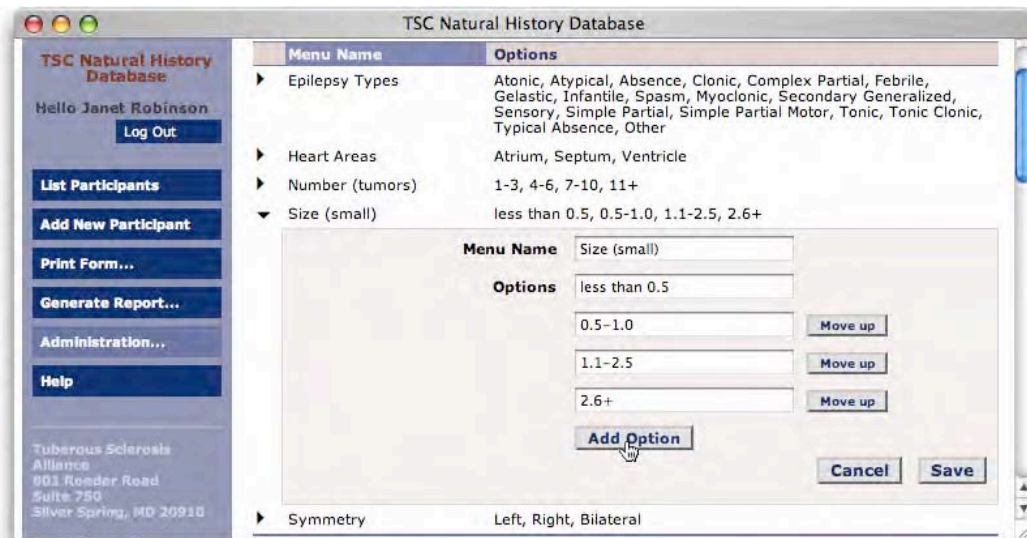
On the *Condition Attribute Menus* screen, administrators may create any number of menus, and once created, these menus can be selected as a *Data Type* for any custom Condition Attribute. In Figure 38, the administrator is now viewing the menu called *Size (small)* that had been assigned in Figure 35.

Figure 38: Condition Attribute Menu (view)



When administrators create or edit a Condition Attribute Menu, they can specify its name and any number of options (selectable menu choices) that should appear in the menu (Figure 39).

Figure 39: Condition Attribute Menus (edit)



RULES

- *Add Option* adds a new empty field to the list, with a *Move Up* button. [Remove buttons too?]

Tests

The dictionary of Tests much simpler than the Conditions dictionary. A Test is simply a name, description, and type (*General* or *Cognitive*). Administrators must create Tests on this screen in order for them to be added to a Participant's record. Only a few representative tests are shown in Figure 40.

Figure 40: Tests (view)

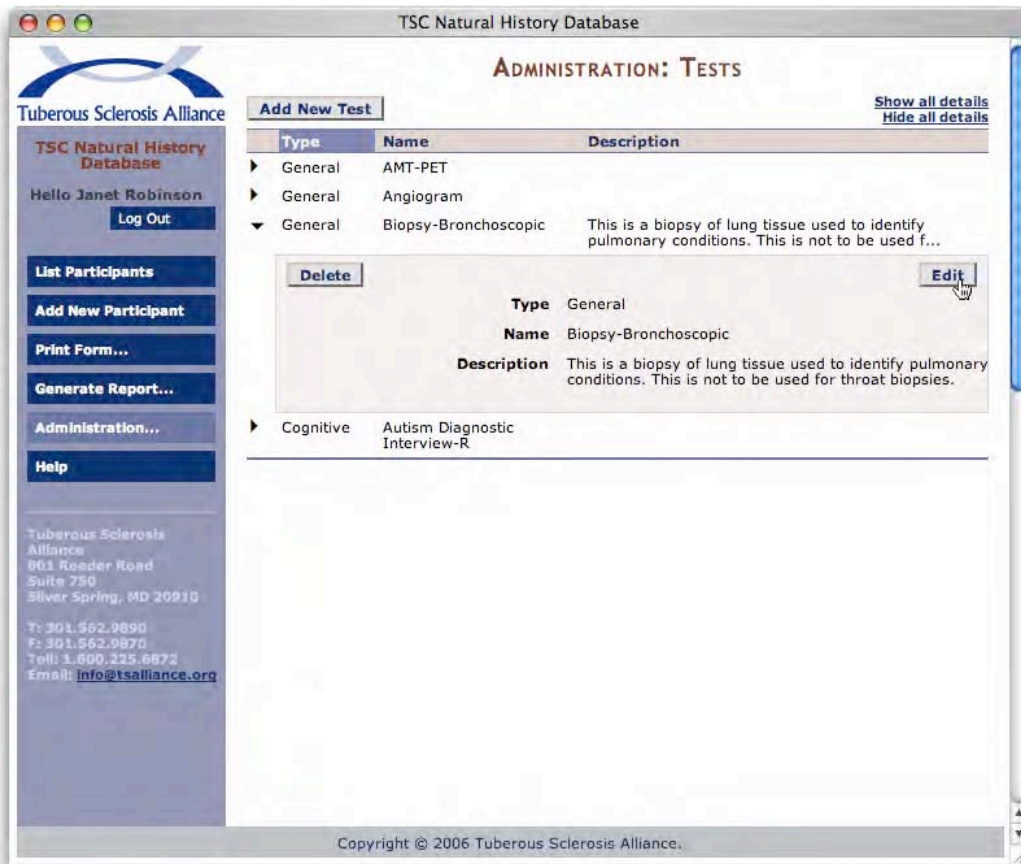
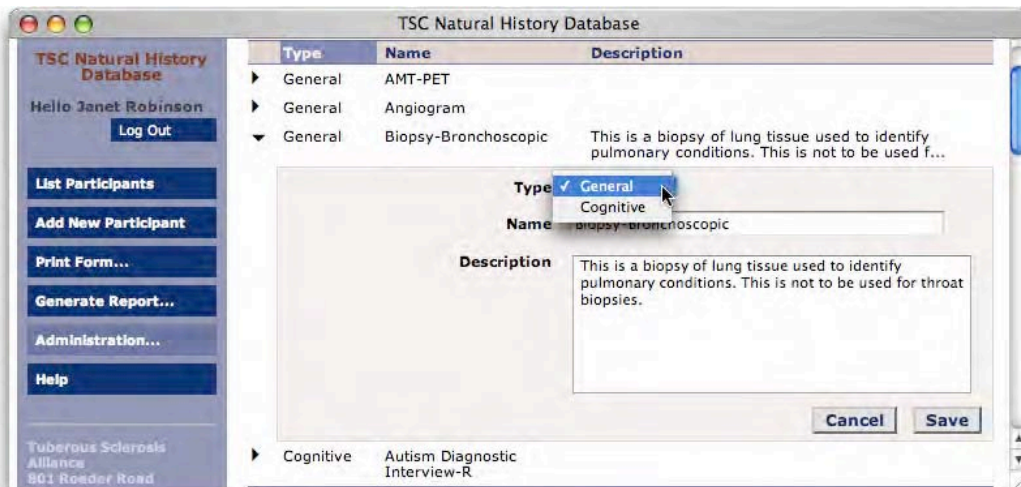


Figure 41: Tests (edit)



Treatments

The Treatments dictionary is structured similarly to the Tests dictionary, except there are four categories of Treatment.

Figure 42: Treatments (view)

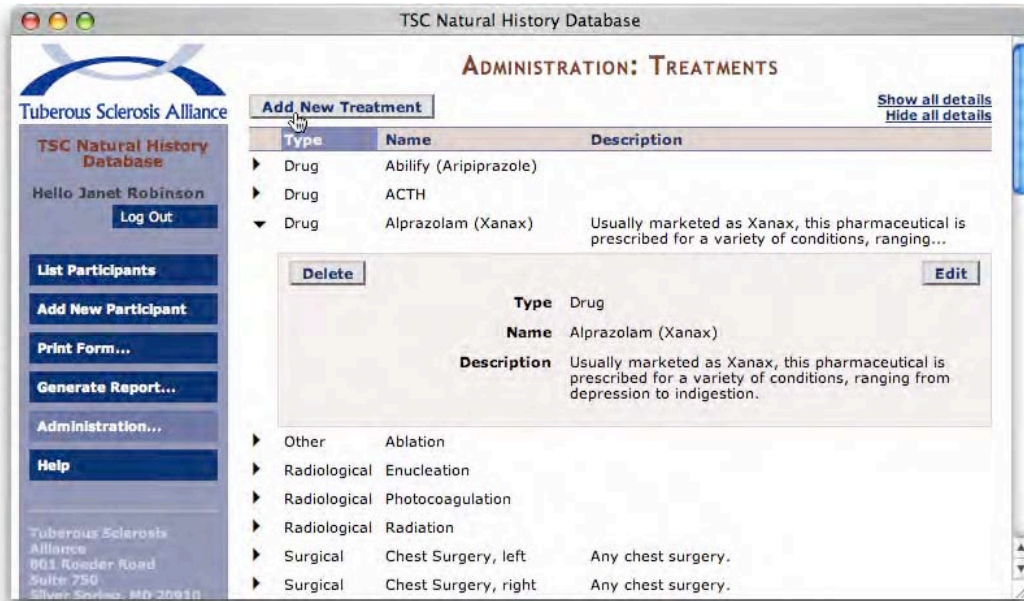
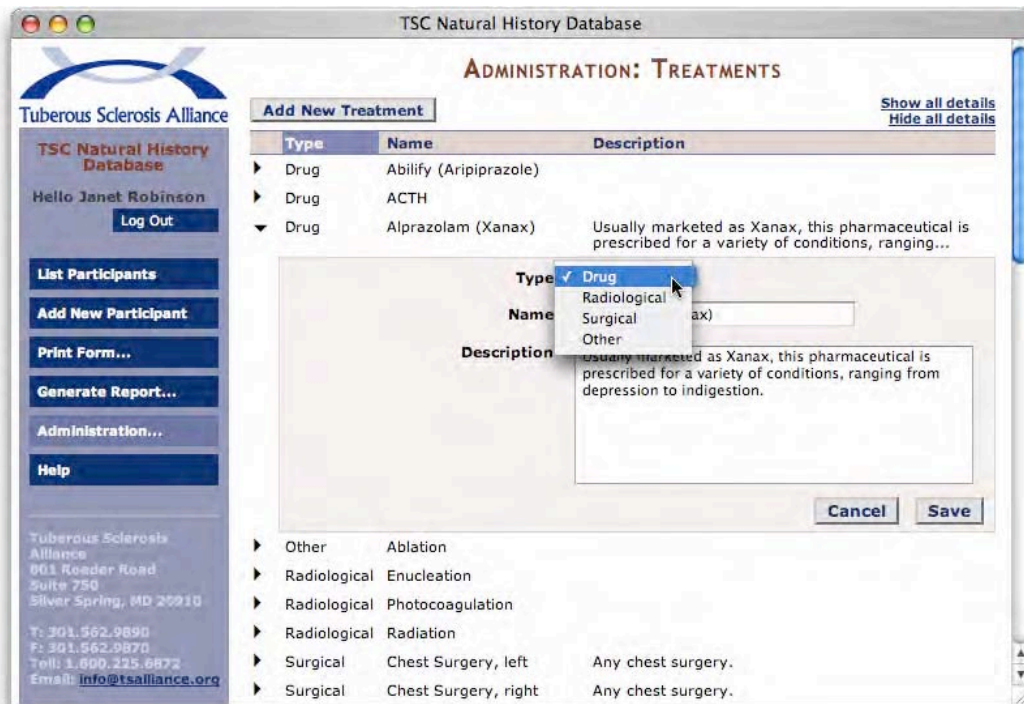


Figure 43: Treatments (edit)



Symptoms

Symptoms are known only by a name and description.

Figure 44: Symptoms (view)

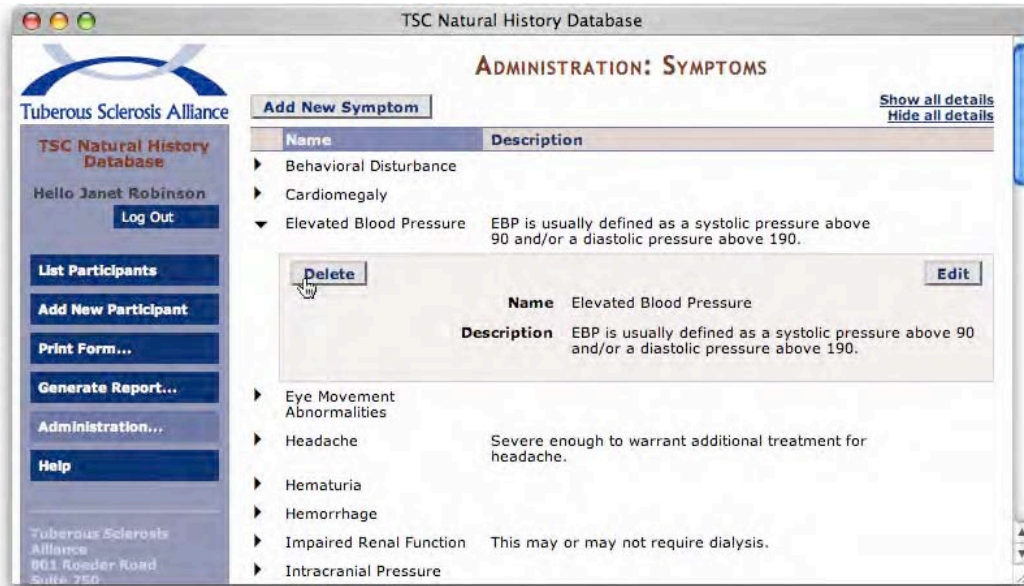
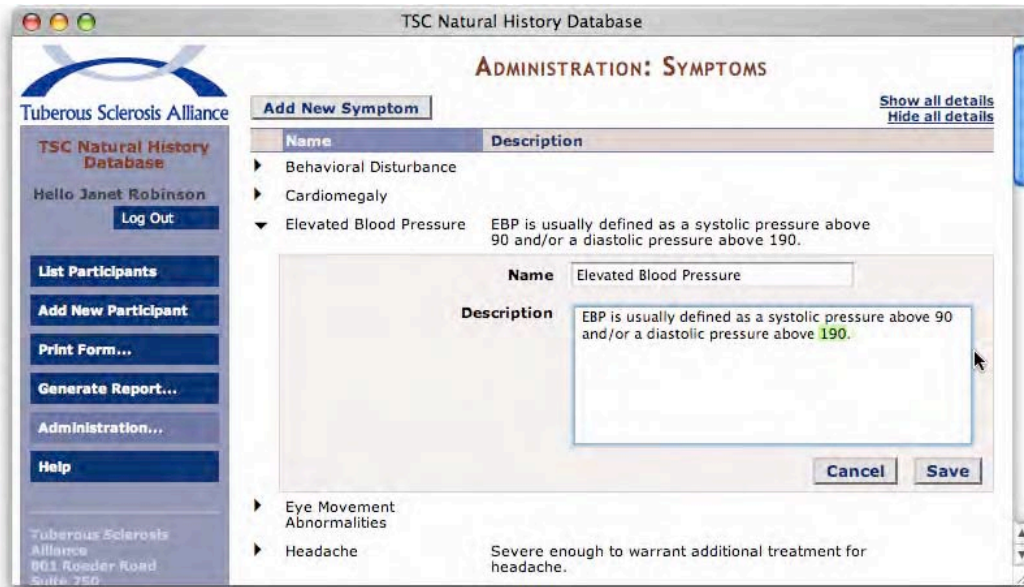


Figure 45: Symptoms (edit)



Data Collection Forms

The database can store any number of data collection forms (usually PDF files designed for printing) that users may access from the user interface. This is done via the Forms > popup menu (Figure 48). In order for forms to appear in this menu, an administrator must upload the PDF file to the database via the Forms screen (Figure 46) accessed from the Administration > popup menu. The Add New Form button causes a system prompt to select an existing file, then the user must give the form a name to be reflected in the Forms > popup menu shown in Figure 48.

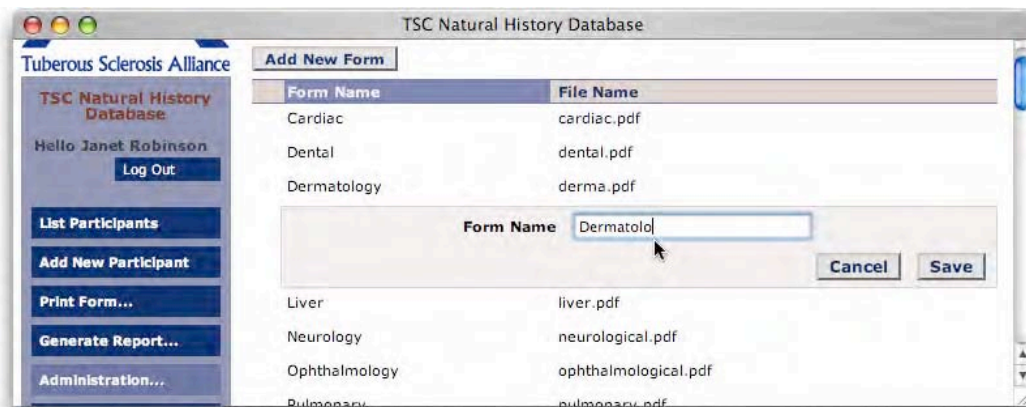
Figure 46: Forms (view)



RULES

- Form Names are used to populate the Forms > menu.

Figure 47: Forms (edit)



PRINTING FORMS

Once a form has been uploaded and named by an administrator, any user may open the form via the Print Form... popup menu (Figure 48). If it is a PDF file, for example, the form will open in a PDF viewer and be available for printing.

Figure 48: Forms Access



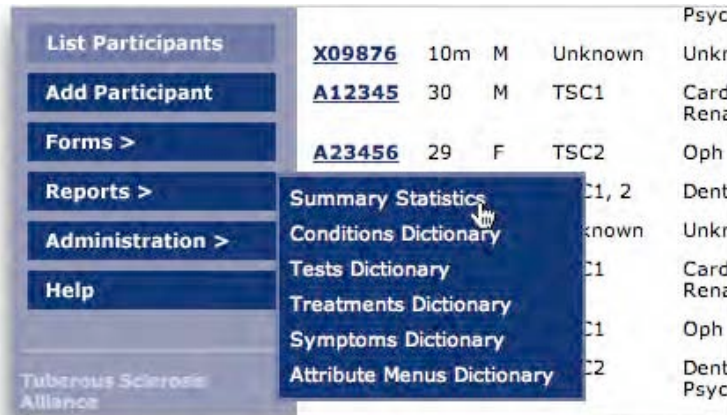
REPORTING

The system can generate four kinds of printable Report: *Participant List*, *Participant Details*, *Summary Statistics*, and *Dictionary Reports*. These Reports are presented in detail in *Chapter 5: Report Design*.

Summary Statistics Report

The Reports > popup menu allows any user to generate a Clinic-by-Clinic statistical summary (local Clinic users will see statistics for their Clinic only; TS Alliance users will see statistics for all Clinics).

Figure 49: Generating Summary Statistics



The *Summary Statistics* report consists of a table formatted for printing from the user's browser.

Participant List Report

Clicking the Print Version link at the top of the *Participants* screen generates a *Participant List* report based on the user's current view of the Participants table. For example, if the *Participants* screen shows only search results, the report will contain only those Participants. If the user has ordered the table by column, the report reflects the user's ordering scheme.

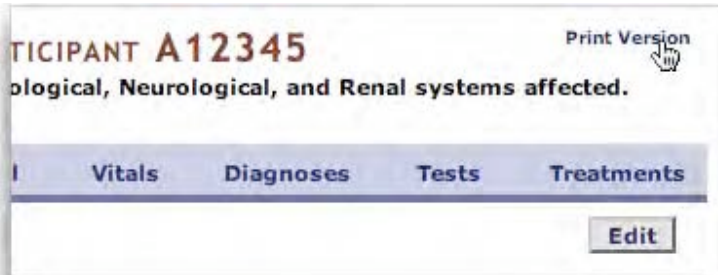
Figure 50: Generating Participant List Reports



Participant Details Report

Clicking the Print Version link at the top of an individual Participant’s record (Figure 51) generates a *Participant Details* report. This report combines the data from all seven tabs into a single printable view.

Figure 51: Generating Participant Details Reports



Although not always shown elsewhere in this chapter, the Print Version link appears above the Participant record regardless of which tab is being viewed.

Dictionary Reports

Five user-configurable medical information dictionaries drive most data collection. To review dictionary contents for administrative purposes, users can generate Reports for each from the Reports > popup menu.

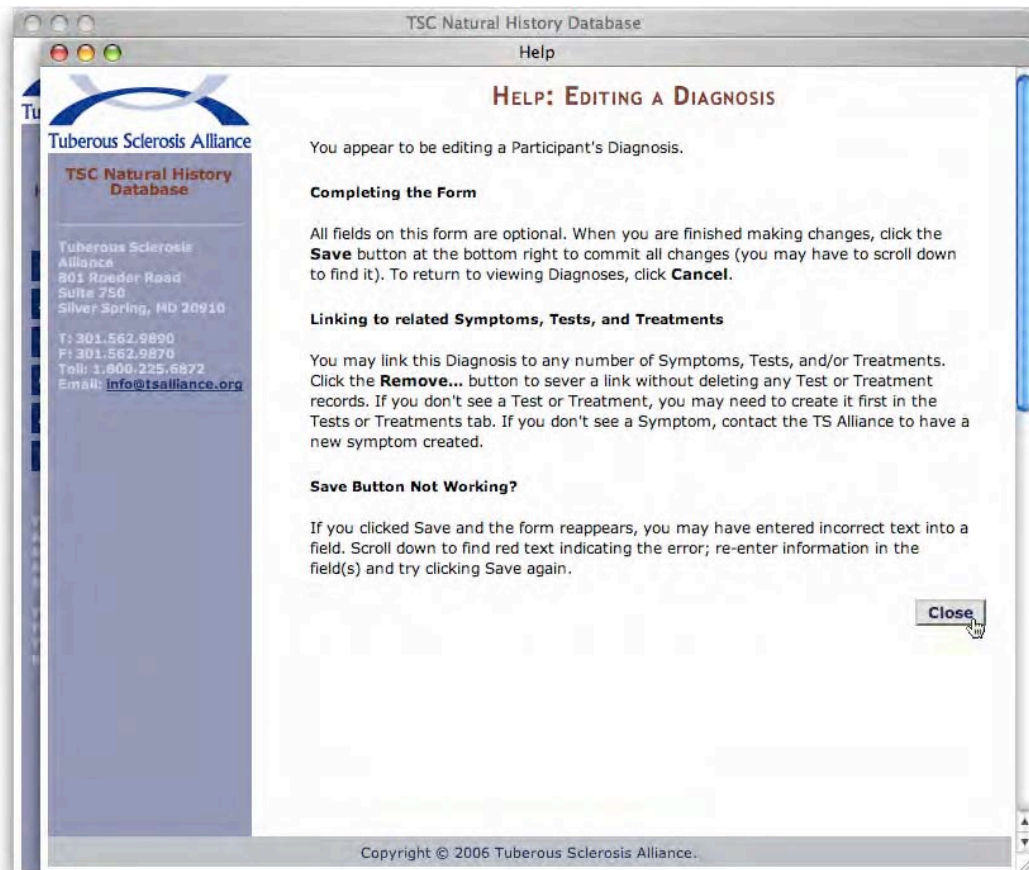
Figure 52: Generating Dictionary Reports



HELP

Clicking the Help button from anywhere in the system will cause a context-sensitive *Help* screen to appear in a new browser window. Figure 55 is a sample; final help screens will be written during the Implementation Phase.

Figure 53: Sample Help Screen



MESSAGES

At times, users may enter inappropriate data into a text field, fail to complete a required field, or attempt other illegal actions that require a specific response from the system. In these cases, the current screen will reappear with an appropriate warning message.

Figure 54: Error/Warning Messages

▼ Cardiac Rhabdomyoma yes 30 Jul 1994 24 Jul 2006 Med record

! Enter a whole number from 1 to 99.

Number *

Location Atrium ▾

Symmetry Left ▾

Size Less than 0.5 ▾ cm

Tissue Bank None.

Symptomatic? Yes No Unknown

Related Symptoms Heart murmur Remove...

Add Symptom... ▾

Appendix M – Revised Statement of Work

Task 1: Set up administrative structure to oversee development of the database (DB)

- Working groups (WG) established November 2003. Several groups have been meeting regularly via teleconferences and will continue to do so. Task was to develop fields to be included in DB by establishing key scientific questions. Focus areas include: Epilepsy/EEG, Brain Lesions/MRI/other CNS Imaging, Dermatology, Renal, Neuropsychological/Behavioral/Cognition, Pulmonary, Genetics/Family History, Other Organ Systems and Registry. A list of WG members will be provided upon request.
- Planning meeting held on April 13, 2004.
- Steering Committee (SC) formally established April 13, 2004.
 - Members are listed in Proposal Body.
- Formation of Advisory Panel. April–August 2004.
 - Names were submitted for review by members of the SC. Contact will be made and members secured by end of August 2004.

Task 2: Drafting and approval of Consortium Agreement

- Consortium Draft copy is included with the Proposal under the Administrative
 - Agreement drafted January 2004.
 - Documentation section.
- Final draft to be circulated between SC, Phase I and Phase II site members. July 2004.
- Approval and signatures to be obtained by the end of July 2004.

Task 3: Development of data fields for DB

- Fields for DB to be developed by Working Groups.
 - January-December 2004.
- WG will also define how to standardize data between clinical sites, e.g., volumetric measurement of cortical tubers on MRI.
 - January-December 2004.
- Teleconferences will be held throughout 2004 to accomplish this task.

Task 4: Meeting of key WG members with Texas Scottish Rite Hospital for Children (TSRHC) Information Technology (IT) staff

- Key WG members, SC members, Advisory Panel and IT staff to finalize data fields.
 - October-November 2004.
- Revised data fields to be circulated to all WG members for final approval.

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- November-December 2004.
- Meeting held to discuss and finalize data fields.
 - December 2004.

Task 5: Transition of administration of project to Tuberous Sclerosis Alliance

- TS Alliance Board of Directors appoints Elizabeth Thiele, M.D., Ph.D., Hope Northrup, M.D. and Vicky Whittemore, Ph.D. to form Steering Committee.
 - Steering Committee will hold monthly conference calls to review progress to date, review protocol and consent forms, respond to questions from vendor, etc.

Task 6: TS Alliance to identify a third-party vendor to develop database.

- Tesuji, Inc. of Denver, Colorado identified and contract negotiated by the TS Alliance for database development project.
 - July 2005

Task 7: Hire director for database project.

- Jo Anne Nakagawa hired by the TS Alliance as the Director of Clinical Projects.
 - October 2005

Task 8: Seek Institutional Review Board approval

- TS Alliance will seek IRB approval for database project. IRB protocol submitted to Independent Review Consulting, Inc. (IRC) in March 2006.
- Revisions requested by IRB, and revised protocol submitted to IRB in May 2006.
- IRB approval received June 13, 2006

Task 9: Tesuji Complete Project Definition Phase.

- Describe the high-level goals and scope of the project.
 - July – August 2005

Task 10: Tesuji Complete Analysis Phase.

- Research agreement on a detailed representation of what the system needs to do (e.g., exactly what data needs to be captured and how that information will get into the database). Two types of analysis will be performed:
 - Domain analysis – identifies the primary “objects” (e.g., people, things, etc.) that the system must know about, their attributes, and their relationships to one another. Status: Done.
 - Workflow analysis – looks at the various processes that the system will participate in.
 - Completed August – December 2005

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Task 11: Tesuji Complete Design Phase.

- Design the user interface and database.
 - User interface consists of screen shots and descriptive text.
 - Database design, or schema, provides a technical view of the database structure.
 - Completed January – July 2006

Task 12: Tesuji Complete Implementation Phase.

- All components described in Task 6 will be built and tested by Tesuji, Inc.
 - July – August 2006

Task 13: Application for Certificate of Confidentiality

- Application will be made to the National Institutes of Health for the DB project on behalf of all TSC Clinics.
 - Submitted on July 13, 2006

Task 14: Meeting of TSC Clinic Directors.

- To be held in conjunction with the TSC National Conference at Indian Lakes Resort
 - Update and review of progress and any issues will be discussed at this meeting.
 - Held July 13, 2006

Task 15: Complete Deployment Phase.

- Database system will be installed on the appropriate servers. Status: Done.
- Training will be provided to TS Alliance staff by Tesuji, Inc. staff.
 - July - August 2006.

Task 16: Drafting and approval of Consortium Agreement

- Consortium Agreement revised.
 - June - August 2006
- Final draft approved by Steering Committee
 - August 2006
- Presented to all TSC Clinic Directors
 - August 2006
- Approval and signatures to be obtained from all participating TSC Clinic Directors
 - September 2006 – June 2007

Task 17: Development of patient recruitment tools

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- Patient recruitment tools to be developed by TS Alliance staff with approval of Steering Committee. July-September, 2006.
 - Tools to include brochures, articles for Perspective (TS Alliance quarterly magazine), TS Alliance website and other materials as yet to be determined.
 - All tools will be submitted for IRB approval prior to use.

Task 18: Development of data collection tools

- Develop data collection forms.
 - July – September 2006
- Meeting with key WG members and SC members to finalize data collection tools.
 - Fall 2006

Task 19: Initiate and complete Pilot Phase.

- All TSC Clinics will be solicited for applications to serve as one of two pilot sites. Status: Solicitation done in April 2006.
- Steering Committee will select two sites in June 2006.
 - Texas Scottish Rite Hospital, Dallas, TX – PI: Steve Sparagana, M.D.
 - Minnesota Epilepsy Group, St. Paul, MN – PI: Michael Frost, M.D.
- Pilot sites will submit protocols for IRB approval at their respective institutions in August 2006.
- TS Alliance staff to train data entry staff at two pilot sites.
 - September – October 2006
- Pilot sites to begin data entry in October 2006 and/or when the protocol is approved by the IRB.
- Intermediate follow-up of progress with data entry to be done by telephone about one month after initiation.
- Data entry to continue at the two pilot sites for six months (until March 2007, or six months following start date).
- TS Alliance will conduct a site visit at the two pilot sites mid-way during the Pilot Phase to ensure regulatory compliance and reliability of database entries and to provide on-site technical support.

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Appendix N – Steering Committee Members (Revised)

David W. Dunn, MD
Associate Professor of Psychiatry and Neurology
Riley Hospital for Children
702 Barnhill Dr., Rm 3701
Indiana Univ. School of Med. - Psychiatry
Indianapolis, IN 46202-5200

Elizabeth Petri Henske, MD
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111-2434

Hope Northrup, MD
Director, Division of Medical Genetics and
TSC Clinic at Memorial Hermann-Texas Medical Center
University of Texas Health Science Center
6431 Fannin Street MSB 3.1444
Houston, TX 77030

Elizabeth A. Thiele, MD, PhD
Director, Carol and James Herscot Center for Adult and
Children with Tuberous Sclerosis Complex
Director, Pediatric Epilepsy Service
Massachusetts General Hospital
175 Cambridge Street, Suite 340
Boston, MA 02114

Vicky Holets Whittemore, PhD
Vice President and Science Director
Tuberous Sclerosis Alliance
801 Roeder Road, Suite 750
Silver Spring, MD 20910

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Appendix O – Central IRB Approval Letter

Independent Review Consulting, Inc.

100 Tamal Plaza, Suite 158, Corte Madera, CA 94925-1418 Phone: 415-485-0717
Mail: P.O. Box 170, San Anselmo, CA 94979-0170 Fax: 415-485-0328

June 27, 2006

Vicky Holtes Whittemore, MD
TS Alliance
801 Roeder Road, Suite 750
Silver Spring, MD 20910

RE: Tuberos Sclerosis Complex (TSC) Natural History Database Project

Dear Dr. Whittemore,

Based on answers to prior questions, the IRB has approved this new study for a period of one year from its initial approval. Your participation as a principal investigator has also been approved. Performance sites are to be approved by their local IRB.

IRB action type & approval number	Full Board 4/11/06 & 6/13/06	06080-01
The sponsor of the study is	Tuberos Sclerosis Alliance	
Expiration date for this study is	Data on gender and ethnic recruitment will be requested.	June 12, 2007
Your principal investigator number	5678-001	
The protocol version ID and/or date	Version 1.4	19 June 2006
Consent form ID and/or date	Consent Version 1.2	Appendix H of the protocol
	Child Assent Version 1.1	Appendix I of the protocol
Advertising/recruitment ID and/or date	Research Flyer	Appendix F of the protocol
	Research Ad 1.1	Appendix G of the protocol
The total number of subjects approved	2,000+	

Principal Investigators are responsible for making sure that studies are conducted according to the protocol *and* for all actions of the staff and sub-investigators with regard to the protocol. As a principal investigator, you have multiple and possibly conflicting responsibilities to the IRB, the research subjects, and the sponsor. If you have questions about them, please feel free to call.

There are five conditions attached to all approval letters:

1. No subjects may be involved in any study procedure prior to the IRB approval date or after the expiration date. (Investigators and sponsors are responsible for initiating Continuing Review proceedings. See IRC's web site at www.irb-irc.net or call us for more details.)
2. All unanticipated or serious adverse events must be reported to the IRB within five working days.
3. All protocol modifications must be IRB approved prior to implementation unless they are intended to reduce risk. This includes any change of investigator, or performance site address.
4. All protocol deviations must be reported to the IRB within five working days.
5. All recruitment materials must be approved by the IRB prior to being used.

Thank you for this submission to IRC and we wish the best for you and your subjects. Please feel free to contact IRC regarding any human subjects questions during the year.

Sincerely,



Penny Wells, Dr.P.H., IRB Chair
(by) Erica J. Heath, MBA, CIP, IRC President

cc: Jo Ann Nakagawa



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Appendix P – Certificate of Confidentiality



National Institutes of Health
National Human Genome
Research Institute
Ethical, Legal, and Social
Implications (ELSI) Research
5635 Fishers Lane, Suite 4076
Bethesda, MD 20892-9305
Telephone: (301) 402-4997
Fax: (301) 402-1950

August 15, 2006

Vicky H. Whittemore, Ph.D.
Vice President and Director of Science
Tuberous Sclerosis Alliance
801 Roeder Road, Suite 750
Silver Spring, MD 20910-4467

Dear Whittemore:

Enclosed is the Confidentiality Certificate protecting the identity of research participants in your project entitled, "*The Tuberous Sclerosis Complex Natural History Database Project.*" Please note that the Certificate expires on August 31, 2016.

Please be sure that the consent form given to research participants accurately states the intended uses of personally identifiable information (including matters subject to reporting) and the confidentiality protections, including the protection provided by the Certificate of Confidentiality, with its limits and exceptions.

If you determine that the research project will not be completed by the expiration date, August 31, 2016, you must submit a written request for an extension of the Certificate three months prior to the expiration date. If you make any changes to the protocol for this study, you should contact me regarding modification of this Certificate. Any requests for modifications of this Certificate must include the reason for the request, documentation of the most recent IRB approval, and the expected date for completion of the research project.

Please advise me of any situation in which the certificate is employed to resist disclosure of information in legal proceedings. Should attorneys for the project wish to discuss the use of the certificate, they may contact the Office of the NIH Legal Advisor, National Institutes of Health, at (301) 496-6043.

Any correspondence should be sent to me at:

Elizabeth J. Thomson, DNSc, RN, CGC, FAAN
Program Director, Ethical, Legal, and Social Implications Research
National Human Genome Research Institute
National Institutes of Health

5635 Fishers Lane, Suite 4076
Bethesda, MD 20892-9305*

*If Express Mailing Use: Rockville, MD 20852

I can also be reached by telephone, fax, or e-mail at:

(301)402-4997

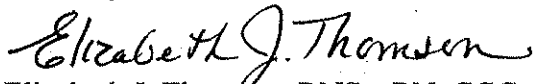
(301)402-1950 fax

e-mail: et22s@nih.gov

web: www.genome.gov/ELSI

Please let me know if there is anything further that you need from me.

Sincerely,



Elizabeth J. Thomson, DNSc, RN, CGC, FAAN
Program Director
Ethical, Legal, and Social Implications Research

Enclosure

Cc: Nancy Taylor ✓
Chief Executive Officer
Tuberous Sclerosis Alliance
801 Roeder Road, Suite 750
Silver Spring, MD 20910-4467



National Institutes of Health
National Human Genome
Research Institute
Ethical, Legal, and Social
Implications (ELSI) Research
5635 Fishers Lane, Suite 4076
Bethesda, MD 20892-9305
Telephone: (301) 402-4997
Fax: (301) 402-1950

CONFIDENTIALITY CERTIFICATE

Number: HG-2006-10

Issued to

Tuberous Sclerosis Alliance

conducting research known as

“The Tuberous Sclerosis Complex Natural History Database Project”

In accordance with the provisions of section 301(d) of the Public Health Service Act 42 U.S.C. 241(d), this Certificate is issued in response to the request of the Principal Investigator, Vicky H. Whittemore, Ph.D., to protect the privacy of research subjects by withholding their identities from all persons not connected with this research. Dr. Whittemore is primarily responsible for the conduct of this research.

Under the authority vested in the Secretary of Health and Human Services by section 301(d), all persons who:

1. are enrolled in, employed by, or associated with the Tuberous Sclerosis Alliance and its contractors or cooperating agencies or units and
2. have in the course of their employment or association access to information that would identify individuals who are the subjects of the research pertaining to the project known as **“The Tuberous Sclerosis Complex Natural History Database Project,”**

are hereby authorized to protect the privacy of the individuals who are the subjects of that research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research.

The goal of this project is to develop a centralized repository for information about a vast number of individuals with tuberous sclerosis complex (TSC) over their lifetime in order to follow the manifestations of the disease over each individual's lifetime; improve the understanding of TSC; utilize the database to identify cohorts of individuals with TSC for

future clinical studies of the different manifestations of the disease; and serve as a resource to TSC researchers to find new treatments and therapies for individuals with TSC.

A Certificate of Confidentiality is needed because potentially sensitive family history and genetic information will be collected during the course of the study. The certificate will help researchers avoid involuntary disclosure that could expose subjects or their families to adverse economic, legal, psychological and social consequences.

To protect participants' confidentiality, the database system will generate and assign a unique five-character identification code to each participant. Each clinic will maintain a separate record of the participant's unique ID and name that is not part of the database. This will be stored in a secure location with access restricted to authorized staff. The database will not contain any names, addresses, social security numbers, or other identifiers that can easily identify the participant. All persons who have access to the database system will sign a confidentiality agreement.

This research begins on September 1, 2006 and is expected to end on August 31, 2016.

As provided in section 301 (d) of the Public Health Service Act 42 U.S.C. 241(d):

"Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

This Certificate does not protect you from being compelled to make disclosures that: (1) have been consented to in writing by the research subject or the subject's legally authorized representative; (2) are required by the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) or regulations issued under that Act; or (3) have been requested from a research project funded by NIH or DHHS by authorized representatives of those agencies for the purpose of audit or program review.

This Certificate does not represent an endorsement of the research project by the Department of Health and Human Services. This Certificate is now in effect and will expire on August 31, 2006. The protection afforded by this Confidentiality Certificate is permanent with respect to any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect.

Date: 8/15/2006 Elizabeth J. Thomson
Elizabeth J. Thomson, DNSc, RN, CGC, FAAN
Program Director
Ethical, Legal, and Social Implications Research

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Appendix Q – Pilot Site Proposal

TSC Natural History Database Project – Six-month Trial Proposal

(Estimated dates: September 2006 – March 2007)

Trial Site: Texas Scottish Rite Hospital for Children, Dallas, Texas

Principal Investigator: Steven P. Sparagana, M. D.

Background:

Members of the Tuberous Sclerosis (TS) Clinic at Texas Scottish Rite Hospital for Children (TSRHC) have a long-standing, deep seated commitment to the care of children with Tuberous Sclerosis Complex (TSC), and to clinical research with this group of children. Members of the TS team have been involved with the TSC Natural History Database Project (DB) dating back to early conversations about the great benefits of such a database. We have been an active force in the development of this DB and are eager to continue our efforts to seeing it rolled out to all the TS clinics.

The TS team at TSRHC helped secure funding from the Department of Defense (DOD) on behalf of the TSA and the TSC Consortium. These funds served as seed money for development of infrastructure necessary to commence development of the DB. With the working groups developed under the auspices of this grant, we helped to develop a data collection tool, which has since been largely incorporated into the electronic data fields created by Tesuji, Inc. (Tesuji). In Fall 2005, our site provided feedback to Tesuji on their further development of the DB. In December 2005, Dr. Sparagana was involved in the DB summit meeting at Indian Lakes Resort in Chicago, and provided helpful feedback to Tesuji, members of the Database Steering Committee and other principals involved in the DB development.

Resources:

Hospital administration at TSRHC has been fully supportive of the creation of the DB and has encouraged us to participate in the DB trial, and in the project once it is rolled out to all the TS clinics. Our Information Systems (IS) department has extensive experience with database creation and maintenance. The IS department was involved in early discussions of development of the DB and is willing to provide technical support at our site, as needed. We have staff in place to manage all phases of the trial, including the IRB proposal and other regulatory paperwork, obtaining consents, interviewing patients and family members, physical examination of patients, chart review, and data entry. Personnel include Dr. Sparagana, two research coordinators, an RN clinical coordinator, several physician assistants, and an administrative assistant.

The TS clinic at TSRHC has a population comprised of about 150 pediatric patients, ages 0 – 18 years. Our families have always shown a willingness to participate in research projects to further their knowledge about TSC, as well as for the greater good. We are certain that the vast majority of our patients would be delighted to participate in both the trial and the full project.

We currently possess computers with internet capability in clinic and non-clinic spaces to facilitate data collection and entry.

Project Specifics:

- We will obtain project approval from the Research Advisory Panel at TSRHC and the local IRB. This will be based on the IRB proposal developed by the TSA, and will include appropriate consent forms and HIPAA documents. The Certificate of Confidentiality obtained by the TSA will also be submitted. This entire process will be completed within 8 – 10 weeks from the time that we are notified that we are a trial participant.
- Catherine Thompson will be the key administrative person who will be involved in set-up and management of the local clinic database user accounts. She will serve as liaison for Tesuji, the TSA, TSRHC TS team members, and TSRHC IS staff.
- Ms. Thompson, another research coordinator (Betsy Teitell, RN), and an administrative assistant (Terry Hurst) will participate in database user training sessions at TSRHC.
- Consent will be obtained from a minimum of 20 patients to participate in the DB trial. Data will be acquired from review of the medical records, interview of the patient and parent(s), and through examination of the patient. Complete data will be entered into the database with the use of existing computer resources. If a patient returns for a clinic visit within the six-month trial period, that data will also be entered. Subject enrollment and data entry will be completed within the six-month trial period. As time and resources permit, additional subjects may be enrolled, as well.
- We will provide feedback to Tesuji and the TSA in the form of immediate calls or e-mails for acute problems, a final report at trial completion, and any interim progress reports deemed necessary.
- We will keep a running log of time and effort spent on the trial by key personnel, and by consultants (e.g. our IS team). This may help the TSA anticipate the time and resources required for data collection set-up at other TS clinics once the project is launched.

Budget:

- A budget of \$3,000 is proposed to help defray the salary expenses of Catherine Thompson, as well as the other administrative support personnel.
- Additionally, supply costs of \$100 are also proposed for miscellaneous consumable project and meeting related expenses.

Tuberous Sclerosis Complex (TSC) National Database (DB)
Annual Report – W81XH-04-0896
PI: Dr. Steven Sparagana

Appendix R– Pilot Site Contract (Draft version)

**TSC NATURAL HISTORY DATABASE PROJECT CONTRACT
TUBEROUS SCLEROSIS ALLIANCE
801 Roeder Road
Suite 750
Silver Spring, MD 20910-4487
(301) 562-9890
1-800-225-6872**

1. Contract Number:

2. Contract Date:

3. Contract Start Date:

4. Contract End Date:

5. Total Amount of Contract:

6. Awarded by: National Tuberous Sclerosis Association, Inc., d/b/a
Tuberous Sclerosis Alliance
(Hereinafter referred to as "TS Alliance")
801 Roeder Road, Suite 750
Silver Spring, MD 20910-4487
Telephone: 301-562-9890
FAX: 301-562-9870

Awarded To:

7. Payments Issued to:

Address:

- 8. Description of Work to be Performed:
 - a. Recruit and enroll individuals with tuberous sclerosis complex at a minimum expected accrual rate of twenty (20) new participants per quarter.
 - b. Collect demographic and genetic information as well as detailed information about conditions affecting the following areas (as applicable): academic, cardiac, cognitive, dental, dermatological, liver, neurological, neuropsychiatric, neuropsychological, ophthalmological, renal, and reproductive.
 - c. Enter information into the web-based database system.

9. Project Work Plan and Schedule: This work will be done over the next six (6) months from [redacted] to [redacted]

10. Description/Specifications: The Contractor (i.e., [redacted]) shall ensure that the necessary personnel and computer with web-access are in place in order to conduct the work described in Section 8.

11. Researcher's Responsibility: The work performed under this contract will be under the direction of the Principal Investigator (PI), [redacted].

12. Contract Compliance: The PI shall, in compliance with this contract, complete the work specified, within the time, sequence, and costs set forth. The work shall be performed in the manner and by the personnel as stated in the attached Database Project Agreement Version 1.6.4.

14. Deliverables:

It is hereby understood and agreed that the total allowable cost of the work effort to be performed under this contract shall not exceed \$15,000.00. It is further understood and agreed that the TS Alliance will not pay any indirect costs (host institution's overhead) costs.

Payments will be made in accordance with the schedule shown below:

Payment #	Amount	Not to Exceed	Date of Payment
#1	_____	<u>Not Applicable</u>	At Initiation (contract signed)
#2	_____	_____	(12 weeks +/- 10 working days after Payment #2)
#3 #3)	_____	_____	(12 weeks +/- 10 working days after Payment #3)

Funds provided under this contract are for the purpose of collecting and entering the data in Section 8 and may not be used for other purposes.

- 15. Other Conditions: In performing the duties under this contract, the Contractor shall:
 - A. Not discriminate in the hiring, promotion, dismissal, or conditions of employment against any person performing work under this contract because

of race, color, religion, national origin, sex, sexual preference, age, handicap, or other characteristic or characteristics unrelated to the performance of work under this contract.

- B. Agree to be responsible for any and all claims, liabilities and losses by whom ever asserted arising out of acts or omissions of the Contractor, the officers, employees, and agents of [REDACTED] in the performance of this Agreement, except those arising by reason of the sole negligence of the TS Alliance, its officers, employees, and agents. In the event of concurrent negligence of the TS Alliance and [REDACTED], its officers, employees, or agents, liability for any and all claims for injuries or damages to persons or property, which arise out of the terms and conditions of this Agreement shall be apportioned under the laws enforced in any courts of competent jurisdiction.
- C. The principal investigator will follow the policies of the attached TS Alliance TSC Database Project Agreement (Version 1.6.4), which include the "Statement of Understanding" (Pages 1-3) and "TSC Natural History Database Access and Usage Policy Manual" (Pages 4-41) The PI's signature on this Contract indicates that the Contract Recipient has read, understood and will follow the policies as they are described in detail in the Policy Manual section of the Agreement, as outlined below.

I PREFACE-DATABASE SYSTEM OVERVIEW

II INSTITUTIONAL REVIEW BOARD APPROVAL AND DATABASE ACCESS

III DATABASE USAGE

IV AUDIT OF DATABASE

V PRESENTATION AND PUBLICATIONS

VI FINANCIAL AGREEMENT

VII TERMINATION OF AGREEMENT

VIII TS ALLIANCE RESEARCH POLICIES

APPENDIX A – G

16. Other Support: The Contractor and Principal Investigator are permitted to seek additional funding from other sources to support the work of this project. The PI should convey information about additional funding support to the Vice President & Director of Science, if applicable.
17. Contractor's Role in Relation to the TS Alliance: While engaged in carrying out and complying with the terms and conditions of this contract, the Contractor is an independent contractor, not an officer, director, employee, or agent of the TS Alliance.

IN WITNESS WHEREOF, the Principal Investigator, Contractor and the TS Alliance agree to the terms of this contract.

Read and Understood By: _____
Principal Investigator (Print or Type Name)

Signature & Date: _____

Read and Understood By: _____
Manager of Contracts and Grants (Print or Type Name)

Signature & Date: _____

Nancy L. Taylor

Read and Understood By: _____
Tuberous Sclerosis Alliance CEO

Signature & Date: _____

Tuberous Sclerosis Complex (TSC) National Database (DB)

Annual Report – W81XH-04-0896

PI: Dr. Steven Sparagana

Appendix S – Database Project Agreement (Draft version)



Tuberous Sclerosis Complex (TSC) Natural History Database Project Agreement

(STATEMENT OF UNDERSTANDING)

To assure that a TSC Clinic Director serving as the site Principal Investigator (hereinafter, "PI") involved with the TSC Natural History Database Project (hereinafter, "DB") knows and understands the policies and operating practices of the Tuberous Sclerosis Alliance (hereinafter, "TS Alliance") regarding access and usage of the database, each PI will be given a copy of the **TSC Natural History Database Access and Usage Policy Manual** (hereinafter, "DB Policies") attesting to his/her acceptance of the policies, which are summarized below.

I **Preface - Database System Overview**

- a. The TSC Natural History Database is a secure, web-based information system that collects and compiles data on individuals who have been diagnosed with TSC. This system is owned and administered by the TS Alliance for the purpose of facilitating TSC research.

II **Institutional Review Board (IRB) Approval and Database Access**

- a. The PI will read and abide to the terms of the **DB Confidentiality Agreement** (Appendix A).
- b. The TS Alliance agrees to provide a copy of the **DB Protocol** and consent templates to the PI for preparation of an IRB application.
- c. The TS Alliance, as Sponsor of the DB, has acquired a **Certificate of Confidentiality** (COC) from the National Institutes of Health (NIH) on behalf of each PI who is involved with the DB.
- d. The TS Alliance will provide a copy of the COC to the PI, who shall ensure that the consent form given to research participants accurately states the intended uses of personally identifiable information and the confidentiality protections, including the protection provided by the COC.
- e. The PI will obtain and maintain in good standing IRB approval to participate in the DB.
- f. The PI may initiate participant recruitment only after receipt of IRB approval.
- g. TS Alliance agrees to provide DB user training for the PI and staff upon receipt of IRB letter from local site approving the DB and their participation in this project.
- h. The **TS Alliance DB Administrator** will set up user accounts and assign DB user access privileges at each TSC Clinic.
- i. The PI and staff will have password-controlled, ongoing access to local participant data.
- j. The **TS Alliance DB Administrator** will have access to all of the data in the DB system.

III Database Usage

- a. The PI shall **inform** the **TSC Database Research Review Committee** (hereinafter, “DBRRC”) in advance of **all** research studies that use **local** participant data, however such studies will not require their review and approval to proceed with the research. The DBRRC will include the members of the **TSC Database Steering Committee** and two TSC Clinic Directors who will serve for a two-year term on a voluntary rotating basis.
- b. All research studies that use **non-local** participant data shall be approved by the DBRRC.

IV Audit of Database

- a. The TS Alliance DB Administrator will conduct periodic audits by telephone and by on site visits.

V Presentations and Publications

- a. The TS Alliance will provide a PI with TS Alliance-approved material about the DB for dissemination at any conference, meeting, media report or interview.
- b. Any material that is written for publication using non-local participant data shall undergo review by the **TSC DB Publications Committee** (hereinafter, “DBPC”), which will be chaired by a senior editor [to be nominated by TSC Clinic Directors and appointed by the TSC Database Steering Committee] and will include the TS Alliance Vice President and Director of Science and two TSC Clinic Directors who will serve on a voluntary rotating basis. The term of service will be determined by the TSC Database Steering Committee.

VI Financial Agreement

- a. A contract will be established between the TS Alliance and the PI’s Institution that will include an initial payment of \$2,500.00 when the DB is deployed at their TSC Clinic. This payment shall be used for DB personnel salary support.
- b. The TS Alliance shall pay Institution on a quarterly basis proportional to the number of new participants enrolled per quarter.
- c. DB Maintenance Fee – The remuneration amount for ongoing entry of participant data after Contract Year 1 is being evaluated during the Pilot Phase (Phase 1). The approved fee schedule will be stated in the Renewal DB Contract for the two TSC Clinics who are in the Pilot Phase and in DB Contracts for TSC Clinics participating in Phase 2 and thereafter.

VII Termination of Agreement

- a. The TS Alliance **may** terminate this Agreement with the PI and Institution if either the PI or the Institution fails to follow the terms described in the Policy Manual or for any other cause. The TS Alliance shall do so by giving the PI 30 days written notice of intent to terminate. (Appendix E)
- b. The PI and Institution may terminate this Agreement at any time by written notification to the TS Alliance at least 30 days prior to intent to terminate. (Appendix E)



- c. The PI will notify local study participants if the DB is terminated for any reason and inform them of other DB locations.

VIII. TS Alliance Policies

- a. The PI and their staff will abide by the TS Alliance policies for:
 - 1. Scientific Misconduct (Appendix F)
 - 2. Intellectual Property (Appendix G)

IX. Certification of PI

This is to certify that I have read the above statement of policies of the TS Alliance regarding access and usage of the TSC Natural History Database, understand it, and agree to abide by it in all matters as they are described in the policy manual. I understand that this Agreement is not transferable to any other PI, Person, Facility, or Institution. If I begin work at a different Institution, I understand that a new Agreement shall be signed. If another PI is named for this project, the new PI will sign a new Agreement. This Agreement shall be renewed **annually in writing**, on or within 30 days of the initial date of signature. Failure to uphold this agreement will result in review of my participation in the DB. The TS Alliance will retain the original signed agreement and you will receive a copy for your records.

PRINCIPAL INVESTIGATOR

INSTITUTIONAL OFFICER

Name (PRINT)

Name (PRINT)

Address

Address

Telephone

Telephone

FAX

FAX

E-MAIL

E-MAIL

Signature

Date

Signature

Date

FOR OFFICE USE ONLY: Appendices signed or completed

(A) REQUIRED
Confidentiality Agreement

(B)
Statement of Assurance

(C)
Research Data Request

(C.1)
Data Query Request
(SHORT FORM)

(D)
Authorship Statement

(E)
Notification of
Intent to Terminate Agreement

TSC NATURAL HISTORY DATABASE ACCESS AND USAGE **POLICY MANUAL**

I PREFACE-DATABASE SYSTEM OVERVIEW

The Tuberous Sclerosis Complex (TSC) Natural History Database (DB) is a secure, web-based information system that collects and compiles data on individuals who have been diagnosed with TSC. This system is owned and administered by the Tuberous Sclerosis (TS) Alliance for the purpose of facilitating TSC research.

II INSTITUTIONAL REVIEW BOARD APPROVAL AND DATABASE ACCESS

a. Confidentiality

All authorized DB users who access information from the DB understand their obligation to keep such information confidential and report violations to the appropriate authorities. As part of this Agreement, the Principal Investigator (PI) shall read and abide by the “TSC Natural History Database Project Confidentiality Agreement” (Appendix A).

b. Certificate of Confidentiality

1. The TS Alliance submitted a multi-site application to the National Institutes of Health (NIH) for a **Certificate of Confidentiality** (hereinafter, “COC”) upon receipt of its Institutional Review Board (IRB) approval of the DB.
 - (a) The initial application was submitted on behalf of the TSC Clinics listed in Appendix A.1.
2. The TS Alliance will provide a copy of the COC to the Director at each TSC Clinic named in the initial application.
 - (a) The TS Alliance will provide a copy of the COC to the Director of a TSC Clinic that is added to the original list of participating sites, upon receipt of their IRB approval for this project.
 - (b) The TS Alliance will provide NIH with an updated list of new participating sites with an assurance that each new site has obtained IRB approval (See Section II.c)
3. The COC protects the PI from being compelled to disclose personal identifying information about a DB participant in any civil, criminal, administrative, legislative, or other proceedings at any level of government.
4. The COC does NOT protect the PI if authorized Department of Health and Human Services (DHHS) representatives request disclosure; or against voluntary disclosure by the PI (NOTE: PI must specify such disclosures in the informed consent form); or if the participant consents in writing to the disclosure.

c. **IRB Approval**

1. The TS Alliance will provide the PI with a copy of the DB Protocol and Consent templates for preparation of the IRB application.
2. The PI agrees to provide a copy of the initial and annual IRB approval letters and approved consent document(s) to the **TS Alliance DB Administrator**.
3. The PI agrees to refrain from initiating participant recruitment and data collection until the **TS Alliance DB Administrator** acknowledges receipt of the IRB approval letter and IRB approved consent documents.
4. The PI agrees to obtain continuing review and/or annual IRB approval prior to its expiration, as long as this Agreement is in effect.
5. The PI agrees to notify the TS Alliance of his/her local IRB approval until written notification is submitted to the TS Alliance stating his/her withdrawal from participation in the DB.
6. The PI will provide written assurance to the TS Alliance that all DB users comply with local IRB regulations pertaining to the Responsible Conduct of Research (involving human beings) by:
 - (a) Providing a copy of a “certificate of completion” of a training course (e.g. web-based or classroom) in the Responsible Conduct of Research for the Director and staff who will participate in recruitment, the consent process, and data entry, or by
 - (b) Completing the “PI Statement of Assurance” Form (Appendix B)

d. **User Access**

1. The **TS Alliance DB Administrator** will set up DB user accounts and assign DB user access privileges.
 - (a) At least one person at each participating TSC Clinic will be authorized to act as a **Local DB administrator** to set up and maintain local clinic user accounts.
 - (b) The **TS Alliance DB Administrator** has authority to remove user access privilege for due cause.
2. A **Clinic DB Entry User** is a person who will have authorization to view, enter, and modify information in the DB.
3. A **Clinic DB Observer User** is a person who will only have authorization to view information in the DB.

4. The **TS Alliance DB Administrator** will have access to all of the data in the DB system in order to review participant data, track the data collection process, generate reports, and share data with DB users at TSC Clinics.
5. A PI with user access privilege will have ongoing access to participant data entered at their local site.
6. User access to the DB will be terminated upon receipt of written notification from the PI of his/her withdrawal from participation in the DB.

III DATABASE USAGE

- a. **Use of Local Participant Data**
The definition of a “local” participant is a person with TSC who is enrolled at the PI’s TSC Clinic. The PI will have ongoing access and use of local participant data.
- b. **Use of Non-Local Participant Data**
The definition of a “non-local” participant is a person who is enrolled at another TSC Clinic. The PI will submit the **Research Data Request Form** (Appendix C) to the TSC Database Research Review Committee to use non-local participant data.
- c. **Use of Data When a Participant Moves from TSC Clinic A to TSC Clinic B**
TSC Clinic A and TSC Clinic B will have access to the participant’s data with the understanding that:
 1. TSC Clinic B shall obtain informed consent from the participant (or his legal representative) to assume primary responsibility for entering information into the database. TSC Clinic A will then be designated as a “Secondary Clinic”.
 2. TSC Clinic B shall contact TSC Clinic A for the Participant’s unique ID number in order to begin entering new information into the DB and to view data entered by TSC Clinic A.
- d. **Use of Data When A Participant is Seen at Multiple TSC Clinics**
 1. Each participant must be identified with only one primary TSC Clinic. The primary TSC Clinic is responsible for entering information from evaluations that are performed at another TSC Clinic that is participating in the DB.
 2. The participant is responsible for having copies of reports of tests or evaluations completed at another TSC Clinic forwarded to the primary TSC Clinic.

IV AUDIT OF DATABASE

- a. **At TS Alliance**
 1. The TS Alliance DB Administrator will audit the database at a minimum frequency of once per month.

- (a) “Audit the database” means that the TS Alliance DB Administrator will access the database and view local participant data to track the number of new participants enrolled; check for informed consent compliance; and monitor user access privileges.
 2. The TS Alliance DB Administrator will conduct periodic telephone calls with the local site DB administrator and/or DB Coordinator to monitor timely entry of data on enrolled participants.
- b. At Local Site**
1. The TS Alliance DB Administrator will conduct periodic on-site audits at a minimum of once per year to review consistency of data entry and to verify informed consent compliance.

V PRESENTATIONS AND PUBLICATIONS

a. General Guidelines

1. The TS Alliance policy concerning presentations and publications resulting from use of non-local participant data is designed to:
 - (a) Assure timely publication of a research study to the appropriate professional audience.
 - (b) Avoid premature publication of results of a research study that might compromise the performance of the study (such as by publication of trends of results before such trends become statistically significant) or that might compromise the ability to publish the results in high quality peer-reviewed journals (as by premature release to the lay press).
 - (c) Maintain high standards of all materials presented or published by the PI.
 - (d) Minimize likelihood of duplicate publication of results by assuring absence of overlap of materials prepared by the PIs.
 - (e) Assure equitable attribution of credit to all of the PIs involved in a specific study
2. To accomplish these ends, it is the policy of the TS Alliance that preparation of all presentations or publications shall be submitted to the TS Alliance for review and approval before presentation or publication.
3. Publications and presentations authored by the TS Alliance will go through the same review process as is the process for each PI (i.e. TSC Clinic Director, other TSC researcher).

b. TS Alliance Approved Materials

The TS Alliance will provide various materials dealing with the DB to a PI upon written request by e-mail, fax or letter.



1. The material prepared by the TS Alliance will be approved by the Chief Executive Officer (CEO).
2. The PI may access this material from the TS Alliance website by user password.
3. Material will include but is not limited to, Microsoft PowerPoint slides; handouts; brochures. The TS Alliance will attempt to update and/or add new material to the Website as needed.

c. **Local Institution**

1. A PI may present TS Alliance approved material dealing with the DB orally and/or by using visual presentation software (such as Microsoft Powerpoint) without prior permission from the TS Alliance at the PI's local Institution or primary workplace.
2. The PI is responsible for obtaining local IRB approval for study-related advertisements and/or recruitment materials, if applicable.

d. **Use of Materials that are not Prepared by the TS Alliance for Media Reports and Interviews**

1. A PI shall obtain written approval from the TS Alliance prior to disseminating any material dealing with any aspect of the DB by magazine, newspaper, radio, or television.
2. Material shall be submitted to the TS Alliance by mail or electronic transmission a minimum of **TEN** (10) days prior to distribution date,
3. The PI is responsible for obtaining local IRB approval for study-related advertisements and/or recruitment materials that are released to the media.

e. **Use of Materials that are not Prepared by the TS Alliance at a Professional Conference or Meeting**

1. A PI shall obtain approval from the TS Alliance prior to disseminating any material dealing with any aspect of the DB at any conference or meeting.
 - (a) Material shall be submitted in **draft or outline** form to the TS Alliance by mail or electronic transmission a minimum of 14 days prior to the conference or meeting date.
 - (b) The TS Alliance will notify the PI by telephone, e-mail, or fax within 7 working days of receipt of material with their decision.
 - i. If the material is deemed unacceptable for presentation, the TS Alliance shall provide recommendations in writing to facilitate the process.

- (c) The PI is encouraged to re-submit material to the TS Alliance for re-review and approval, however the TS Alliance cannot guarantee a decision if the material is received too close to the conference or meeting date.
- (d) The PI shall provide a copy of the final presentation to the TS Alliance within five days of the end of the conference or meeting.

f. **Publications**

1. The PI or Lead Author shall submit any material/manuscript that is written for publication using local and non-local participant data to the **TSC DB Publications Committee (DBPC)** for review and approval.
 - (a) The **DBPC** will be chaired by a senior editor with a three-member committee composed of the TS Alliance Vice President and Director of Science, and two TSC Clinic Directors.
 - i. **DBPC Senior Editor:** The TSC Database Steering Committee will appoint this person from names that the TSC Clinic Directors submit to them. The term of service will be determined by the TSC Database Steering Committee.
 - ii. **DBPC members:** Two TSC Clinic Directors will serve on a voluntary rotating basis. The term of service will be determined by the TSC Database Steering Committee.
2. The DBPC will notify the PI or Lead Author in writing within 30 days of receipt of material with one of the following:
 - (a) **A Full Approval Letter** will be issued when the material or manuscript satisfactorily meets the DBPC Publication Guidelines (to be developed); or the PI or Lead Author are encouraged, but not required, to make suggested content changes prior to submitting it for publication.
 - (b) **An Approvable Letter** will be issued when the material or manuscript will meet DBPC Publication Guidelines (to be developed) if (1) suggested changes are made and/or (2) a request for additional information is satisfactorily answered. The PI or Lead Author is invited to re-submit material or manuscript to the DBPC within **30 days** of receiving the Approvable Letter to obtain a **Full Approval Letter**. See **Right to Disagree**, below.
 - (c) **An Unapprovable Letter** will be issued when the material or manuscript does not meet the DBPC Publication Guidelines (to be developed), and/or substantive revisions to the content are recommended and therefore unacceptable for publication as submitted. The PI or Lead Author is invited to re-submit material or manuscript to the DBPC within **60 days** of receiving the Unapprovable Letter for reconsideration. See **Right to Disagree**, below.

- (d) **Right to Disagree:** The PI or Lead Author may submit a rebuttal letter. The DBPC will review correspondence in the order of receipt at the TS Alliance.

g. **Authorship and Credit**

1. **General Guidelines:** Authorship credit should be based on substantial contribution to (1) conception and design or analysis and interpretation of the data; and (2) drafting the manuscript or revising it critically for important intellectual content. In accordance with accepted practice, each author will be required to sign a statement that s/he has (1) participated sufficiently in the work to take public responsibility for the content, (2) contributed significantly to the work upon which the manuscript is based, and (3) read, understands and approves of the final version to be published. (Appendix D)
2. **Authorship Boilerplate**
 - (a) A manuscript that uses non-local participant data will use the **DB Authorship Boilerplate** shown below:

The TSC Natural History Database Project*

*A complete list of participants involved in the collection of the reported data is presented in the acknowledgements section.

- (b) A manuscript that uses only local participant data does not require the DB Authorship Boilerplate, but should acknowledge the TS Alliance and the DB.

VI **FINANCIAL AGREEMENT**

a. **Project Support**

1. The TS Alliance shall announce the amount of funds available for project support on or by June 30th each year. The amount awarded to a PI will be determined annually through the TS Alliance's annual budget process.
2. The TS Alliance will provide a PI's Institution with an initial payment of when the DB is deployed at their TSC Clinic through a contract with the Institution. This payment shall be used towards DB personnel salary support (i.e. a data entry user).
3. Additional salary support will be paid on a quarterly basis as defined in Section V.b.
4. Funds will be dispersed on a quarterly basis on or about the 1st of September, December, March, and June or as specified in the Contract.

b. **Payment Schedule**

1. Each quarterly payment will be determined based on the number of new participants enrolled during each 12-week recruitment period.

- i. “Participant enrolled” means that a valid consent is on file at the investigator’s site, and “pertinent medical information” is entered into the web-based database system.
 - (1) A “valid consent” means that informed consent has been obtained per institutional review board guidelines.
 - (2) “Pertinent medical information” means demographic and genetic information, as well as detailed information about conditions in the following areas (as applicable to the participant): academic, cardiac, cognitive, dental, dermatological, liver, neurological, neuropsychiatric, neuropsychological, ophthalmological, renal, and reproductive.
 - ii. “Recruitment period” means a fixed time period during which the TS Alliance Database Administrator will monitor new participant enrollment.
 - iii. The First recruitment period (12-weeks) will start on the Monday following the date the contract is signed.
2. The TS Alliance Database Administrator will query the DB within 5 working days after the end of each recruitment period and generate a report of the number of new participants enrolled during this period.
 3. A fixed amount of \$300.00 will be paid to the PI’s Institution for each new participant enrolled, not to exceed the maximum quarterly payment specified in the Contract.
 4. The total amount due will be paid (i.e. check will cut) at or within 10 working days after the end of each recruitment period.
 5. All payment may be withheld if no work has been completed.
 - (a) The TS Alliance may require that the initial payment of \$2,500.00 be returned if:
 - i. Participants have been enrolled but no pertinent medical information (as defined in Section V.b.1.i(2)) for these participants has been entered into the database.
 - ii. Participants have been enrolled but entry of pertinent medical information (as defined in Section V.b.1.i(2)) into the database is incomplete (e.g. There is pertinent medical information documented on **TSC Database Forms**, which have not been entered into the database.)
- c. **Payment for Ongoing Data Entry**
- The remuneration amount for ongoing entry of participant data after Contract Year 1 is being evaluated during the Pilot Phase (Phase 1). The approved fee schedule will be stated in the Renewal DB Contract for the two TSC Clinics who are in the Pilot Phase and in DB Contracts for TSC Clinics participating in Phase 2 and thereafter. The approved **Fee Schedule** for ongoing data entry will replace the aforementioned text.

d. **Additional Support**

1. The TS Alliance may continue to seek grants that will help provide salary support for data entry personnel.
2. The TS Alliance encourages the PI to submit grants from other sources that utilize the DB and provides support for the DB, as well as staff, clinicians, research tests, and/or new software programming. The TS Alliance should be informed of all such grant applications, and support for the DB effort included in the annual budget of the grant application. All requests for support that include the DB should be reported to the TS Alliance prior to submission of the application to check for any potential overlap in research and funding.

VII **TERMINATION OF AGREEMENT**

- a. The TS Alliance may terminate this Agreement with the PI and Institution if either the PI or the Institution fails to uphold the terms described in the Policy Manual. The TS Alliance shall do so by giving the PI and Institution 30 days written notice of intent to terminate.
- b. The TS Alliance will consider any matters submitted in writing by the PI and/or Institution in response to the above notice, and may place the PI on probationary status in order for him/her to resolve minor violations.
- c. The PI and Institution may terminate this Agreement at any time by written notification to the TS Alliance at least 30 days prior to intent to terminate. (Appendix E)
- d. The TS Alliance Administrator shall cancel DB user access of all individuals at the Institution on the termination date.
- e. The TS Alliance as owner of the DB retains control of the data stored in the DB and will have the right to use the data themselves. The TS Alliance will acknowledge the PI/Institution in any publication or presentation in which their data is used.
- f. Individual study participants entered through a terminated site will be informed of the termination and location of other participating sites.

VII. **TS ALLIANCE RESEARCH POLICIES**

- a. All PIs and their staff will read and abide by the TS Alliance policies for:
 1. Scientific Misconduct (Appendix F)
- b. Intellectual Property (Appendix G)



Appendix A

TSC Natural History Database Project CONFIDENTIALITY AGREEMENT

IMPORTANT: PLEASE READ THIS ENTIRE AGREEMENT. IF YOU HAVE ANY QUESTIONS, PLEASE ASK THEM BEFORE SIGNING. THE TUBEROUS SCLEROSIS ALLIANCE WILL RETAIN THE ORIGINAL SIGNED AGREEMENT AND YOU WILL RECEIVE A COPY FOR YOUR RECORDS.

Information about individuals with tuberous sclerosis complex (TSC) in any form is considered sensitive and private. All who acquire access to such information will, by signing this Agreement, acknowledge and understand their obligation to keep such information confidential and report violations to the appropriate authorities.

GENERAL AGREEMENT: During the course of my duties with, TESUJI, INC. or TSC Clinic or Tuberous Sclerosis Alliance (Circle Applicable Entity)

(IF TSC CLINIC, Please Print Name Here)

I may receive or have access to static or video images, or verbal, written or computer generated information concerning patients with TSC. I agree that, except as authorized or directed by Tuberous Sclerosis Alliance or by legal process, I will not at any time during or after my tenure disclose any such information to any person, or permit any person to examine or make copies of any documents prepared by me, coming into my possession or control, or to which I have access. I understand that unauthorized access or disclosure by me may result in an inquiry or disciplinary action, up to and including termination, and civil or criminal penalties, or both.

COMPUTER ACCESS AGREEMENT: I recognize and acknowledge that computer access privileges require unique responsibilities for care and security. Therefore, I agree to the following:

- I will keep my database access password confidential and not share it with anyone, except the administrator or allow anyone to use my password to access the TSC Natural History Database Project, nor will I use another person's password.
- I will use my TSC Natural History Database Project access password solely to perform duties with a clear need-to-know criterion.
- I will not knowingly enter or attempt to enter false information into the TSC Natural History Database.
- I will use appropriate sign-off procedures when leaving a common-use computer workstation.
- I will not create or modify any software for the purposes of disrupting operations; circumventing security controls; destroying or falsifying data; providing unauthorized access to the database; or gaining access to database systems for which I am not authorized.

I HAVE READ ALL OF THE SECTIONS OF THIS AGREEMENT AND I UNDERSTAND AND AGREE TO ABIDE BY THEM.

Signature _____ Date _____

Name (Please Print) _____

Appendix A.1

LIST OF TSC CLINICS

The following list represents the TSC Clinics that were included in the initial TS Alliance application to the NIH for a Certificate of Confidentiality.

State	Participating Unit	Address	Project Director
California	The TS Clinic at Loma Linda University Children's Hospital	11175 Campus Street Loma Linda, CA 92350	Stephen Ashwal, MD
	The TSC Clinic at UCLA	10833 Le Conte Avenue, 22-474 MDCC Los Angeles, CA 90095-1752	Susan Koh, MD Joyce Wu, MD (Co-Directors)
	Jack & Julia Center for TSC	Children's Hospital & Research Center at Oakland 747 52 nd Street Oakland, CA 94609	Candida M. Brown, MD
Connecticut	Neurogenetics Clinic at Connecticut Children's Medical Center	282 Washington Street Hartford, CT 06101	Francis J. DiMario, MD
District of Columbia Metro Area	TS Clinic at Children's National Medical Center	8501 Arlington Blvd. Suite 200 Fairfax, VA 22031	William McClintock, MD
Florida	Miami Children's Hospital	3200 S.W. 60 th Court Miami, FL 33155	Michael Duchowny, MD
Illinois	The University of Chicago Comer Children's Hospital Neurogenetic Clinic	5841 S. Maryland Chicago, IL 60637	Michael H. Kohrman, MD
Massachusetts	Multidisciplinary TS Program at Children's Hospital Boston	300 Longwood Avenue Boston, MA 02115	Mustafa Sahin, MD, PhD
	The Carol and James Herscot Center for Children and Adults with TSC	Massachusetts General Hospital 175 Cambridge Street Boston, MA 02114	Elizabeth A. Thiele, MD, PhD



State	Participating Unit	Address	Project Director
Michigan	Children's Hospital of Michigan	3901 Beaubien Detroit, MI 48201	Harry T. Chugani, MD
Minnesota	TSC Clinic without Walls, a branch of the Minnesota Epilepsy Group & Children's Hospital and Clinics of St. Paul	310 Smith Avenue N. Suite 300 St. Paul, MN 55125	Michael Frost, MD
Missouri	TS Clinic at Children's Hospital St. Louis	One Children's Place St. Louis, MO 63110	Michael Wong, MD, PhD
New York	The Tuberous Sclerosis Center at New York University Medical Center	403 East 34 th Street 4 th Floor Rivergate Building New York, NY 10016	Josiane LaJoie, MD
Ohio	TS Clinic at Cincinnati Children's Medical Center	3333 Burnet Avenue Cincinnati, OH 45229-3039	David N. Franz, MD
Pennsylvania	University of Pennsylvania Medical Center	3400 Spruce Street Philadelphia, PA 19104	Peter Crino, MD, PhD Katherine L. Nathanson, MD (Co-Directors)
	TS Clinic at Children's Hospital Pittsburgh	3705 Fifth Avenue Pittsburgh, PA 15208	Deborah Holder, MD
Texas	The TS Clinic at Texas Scottish Rite Hospital for Children	2222 Welborn Street Dallas, TX 75219-3924	Steven P. Sparagana, MD

DB Project Agreement Version 1.6.4 Appendix A.1 (TSC Clinics)

APPENDIX B

PI STATEMENT OF ASSURANCE
“Responsible Conduct of Research (RCR) Training”

INSTRUCTIONS: List each person who will assist the PI in the TSC Natural History Database Project. Include Role, and Completion Date of RCR Training (or similar training offered and/or approved by the local IRB)

PRINT NAME	ROLE (i.e. PI, co-investigator, nurse coordinator, data entry)	COMPLETION DATE OF RCR TRAINING
(PI)		

I assure the TS Alliance that the above named persons have completed RCR Training or a similar program as offered or approved by my local IRB.

Signature of PI Date



Appendix C

RESEARCH DATA REQUEST FORM

INSTRUCTIONS: Researchers who wish to access information from the *TSC Natural History Database* must submit this **REQUEST FORM** to the **TSC Database Research Review Committee** for approval. Please be sure that you have completed both Sections. **Incomplete Requests will not be considered.**

SECTION A – GENERAL INFORMATION

PRINCIPAL INVESTIGATOR NAME	
NAME OF INSTITUTION	
DEPARTMENT	
ADDRESS	
CITY, STATE, ZIP	
TELEPHONE	
FAX	
E-MAIL	
RESEARCH PROPOSAL TITLE	
IRB APPROVED?	YES [<input type="checkbox"/>], IF YES, APPROVAL PERIOD IS: NO [<input type="checkbox"/>]

CONFIDENTIALITY AGREEMENT:

I understand that the TS Alliance will share data from the TSC Natural History Database if the TSC Database Research Review Committee (DBRRC) approves my research proposal. I agree that the information I receive is to be considered confidential and that I will not disclose, publish, or reveal any information without written permission from the TSC Database Research Review Committee.

Principal Investigator Signature

Date

FOR OFFICE USE ONLY:	
PROPOSAL RECEIVED ON: _____	ID NO. _____
DATE SENT TO DRRC: _____	BY WHOM: _____
DRRC DECISION: [<input type="checkbox"/>] APPROVED [<input type="checkbox"/>] NOT APPROVED	
OTHER: _____	



SECTION B – RESEARCH PROPOSAL

Please limit your proposal to three double-spaced pages, which should include the following sections:

- I BACKGROUND** Include a clear and concise evaluation of existing knowledge and specifically identify what new information your project intends to add.
- II RATIONALE** Provide a basis for your proposed research project.
- III DATA ANALYSIS** Describe the proposed methodology and a power analysis to demonstrate that the data set is large enough to provide statistically significant results.
- IV REFERENCES** List any relevant references that support your rationale and study design.



Appendix C.1

NON-LOCAL DATA QUERY REQUEST – SHORT FORM

USE THIS SHORT FORM TO REQUEST SUMMARY INFORMATION OF NON-LOCAL DATA FROM THE TSC NATURAL HISTORY DATABASE TO HELP YOU DETERMINE IF A RESEARCH STUDY IS WORTH PROPOSING.

GENERAL INSTRUCTIONS: Researchers who wish to access non-local information from the *TSC Natural History Database* must submit this **REQUEST FORM** to the **TSC Database Administrator**. Please be sure that you have completed both Sections. **Section A must be complete with signature and date before Request is processed.**

SECTION A – GENERAL INFORMATION

RESEARCHER NAME	
NAME OF INSTITUTION	
DEPARTMENT	
ADDRESS	
CITY, STATE, ZIP	
TELEPHONE	
FAX	
E-MAIL	

CONFIDENTIALITY AGREEMENT:

I agree that the information I receive is to be considered confidential and that I will not disclose, publish, or reveal any information without written permission from the TS Alliance.

Researcher Signature

Date

FOR OFFICE USE ONLY:	
DATA QUERY REQUEST RECEIVED ON: _____	ID NO. _____
DATE SENT TO RESEARCHER _____	BY WHOM: _____
OTHER: _____	

TUBEROUS SCLEROSIS ALLIANCE NATURAL HISTORY DATABASE PROJECT / NON-LOCAL DATA QUERY REQUEST – SHORT FORM



SECTION B – DATA QUERY REQUEST

INSTRUCTION: Please use the template below to submit your data query.

FIND PARTICIPANTS

Initial Search Criteria		Add To These Results
Of Minimum Age		
Of Maximum Age		
Initial Search Criteria		Add To These Results
With an Affected Area	<input type="checkbox"/> Academic <input type="checkbox"/> Cardiac <input type="checkbox"/> Dental <input type="checkbox"/> Dermatological <input type="checkbox"/> Liver <input type="checkbox"/> Neurological <input type="checkbox"/> Neuropsychiatric <input type="checkbox"/> Neuropsychological <input type="checkbox"/> Ophthalmological <input type="checkbox"/> Pulmonary <input type="checkbox"/> Renal <input type="checkbox"/> Reproductive <input type="checkbox"/> Other (specify)	<input type="checkbox"/> Academic <input type="checkbox"/> Cardiac <input type="checkbox"/> Dental <input type="checkbox"/> Dermatological <input type="checkbox"/> Liver <input type="checkbox"/> Neurological <input type="checkbox"/> Neuropsychiatric <input type="checkbox"/> Neuropsychological <input type="checkbox"/> Ophthalmological <input type="checkbox"/> Pulmonary <input type="checkbox"/> Renal <input type="checkbox"/> Reproductive <input type="checkbox"/> Other (specify)
Diagnosis Specify		
With a Variation of Type	<input type="checkbox"/> Mutation <input type="checkbox"/> Polymorphism <input type="checkbox"/> Unknown	
In Gene	<input type="checkbox"/> TSC 1 <input type="checkbox"/> TSC 2	
With Expression Type	<input type="checkbox"/> Missense <input type="checkbox"/> Nonsense <input type="checkbox"/> Silent	
With Base Change Type	<input type="checkbox"/> None <input type="checkbox"/> Insertion <input type="checkbox"/> Deletion <input type="checkbox"/> Substitution <input type="checkbox"/> Rearrangement	

TUBEROUS SCLEROSIS ALLIANCE NATURAL HISTORY DATABASE PROJECT / NON-LOCAL DATA QUERY REQUEST – SHORT FORM



Initial Search Criteria		Add To These Results
Who received Treatment of Type	<input type="checkbox"/> Drug, _____ (specify sub-category) <input type="checkbox"/> Psychological <input type="checkbox"/> Radiological <input type="checkbox"/> Surgical <input type="checkbox"/> Other	<input type="checkbox"/> Drug, _____ specify sub-category) <input type="checkbox"/> Psychological <input type="checkbox"/> Radiological <input type="checkbox"/> Surgical <input type="checkbox"/> Other
Treatment specify		
In Time Frame	<input type="checkbox"/> Currently Receiving <input type="checkbox"/> Received in the Past	<input type="checkbox"/> Currently Receiving <input type="checkbox"/> Received in the Past
Who have Related Participants	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
Who were recruited for Study	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
With current Status	<input type="checkbox"/> Invited <input type="checkbox"/> Enrolled <input type="checkbox"/> Declined	<input type="checkbox"/> Invited <input type="checkbox"/> Enrolled <input type="checkbox"/> Declined
Who have Mortality Status	<input type="checkbox"/> Living <input type="checkbox"/> Deceased	*NOTE: Request will be processed upon faxed receipt of Page 1 with researcher's signature and date

Submit this Request Form by e-mail*, FAX, or mail to:

TS Alliance TSC Database Administrator
 801 Roeder Road, Suite 750
 Silver Spring, MD 20910
 FAX (301) 562-9870



Appendix D

AUTHORSHIP STATEMENT

Manuscript Title: _____

Corresponding Author: _____

Authorship Criteria. All persons listed as authors must meet all of the following criteria.

- I have participated sufficiently in the work to take public responsibility for the content.
- I have contributed significantly to
 - a. Conception and design or analysis and interpretation of the data, and to
 - b. Drafting the article or revising it critically for important intellectual content, and I have read and approved the final version to be published.

Author Signature

Date Signed

Author's Name (PRINT)



APPENDIX E

NOTIFICATION OF INTENT TO TERMINATE TSC DATABASE PROJECT AGREEMENT

PARTY SUBMITTING THIS NOTIFICATION: (TICK APPLICABLE BOX)

- THE TS ALLIANCE TSC CLINIC DIRECTOR (PI) and INSTITUTION

This is to notify (TICK APPLICABLE BOX):

- THE TS ALLIANCE
- TSC CLINIC DIRECTOR (PI) _____

PRINT NAME

OF MY/OUR INTENT TO TERMINATE THIS AGREEMENT EFFECTIVE ON:

PRINT DATE
(DATE SHALL BE AT LEAST 30 DAYS AFTER SUBMISSION OF THIS NOTIFICATION)

SIGNATURE

DATE



Appendix F

SCIENTIFIC MISCONDUCT POLICY

(TS ALLIANCE POLICY FOR RESPONDING TO ALLEGATIONS OF SCIENTIFIC MISCONDUCT)

I. INTRODUCTION

- A. GENERAL POLICY:** THE TUBEROUS SCLEROSIS ALLIANCE (TS ALLIANCE) WILL NOT TOLERATE SCIENTIFIC MISCONDUCT BY ANY TS ALLIANCE GRANT RECIPIENTS, GRANT APPLICANTS, OR BY EMPLOYEES INVOLVED IN CARRYING OUT WORK, WHICH IS SUPPORTED, BY THE PUBLIC HEALTH SERVICE (PHS) OR OTHER FUNDING AGENCIES. THE TS ALLIANCE SUPPORTS THE HIGHEST LEVEL OF SCIENTIFIC INTEGRITY, AND WILL MAKE EVERY ATTEMPT TO PREVENT MISCONDUCT IN RESEARCH. IN ADDITION, THE TS ALLIANCE WILL SUPPORT GOOD FAITH WHISTLEBLOWERS SO THAT THEIR REPUTATIONS AND/OR CAREERS ARE NOT DAMAGED BECAUSE THEY PROVIDE ALLEGATIONS OF SCIENTIFIC MISCONDUCT.
- B. Scope:** This policy and the associated procedures apply to all individuals at the TS Alliance and the TS Alliance-funded researchers who are employed by other institutions. This policy applies to any person paid by, under the control of, or affiliated with the TS Alliance, as well as to individuals at other institutions who are involved with TS Alliance-funded researchers, such as scientists, trainees, technicians and other staff members, students, fellows, guest researchers, or collaborators. This policy also applies to any individual who submits a Letter of Intent and/or grant application to the TS Alliance requesting funding from the organization.

The policy and associated procedure will normally be followed when an allegation of possible misconduct in science is received by an employee of the TS Alliance. Particular circumstances in an individual case may dictate variation from the normal procedure deemed in the best interests of TS Alliance, the Institution, or the PHS. Any change from normal procedures also must ensure fair treatment to the subject of the inquiry or investigation. Any significant variation should be approved in advance by the Chief Executive Officer of the TS Alliance.

II. Definitions

- A. *Allegation*** means any written or oral statement or other indication of possible scientific misconduct made to a TS Alliance official.
- B. *Complainant*** means a person who makes an allegation of scientific misconduct.
- C. *Conflict of interest*** means the real or apparent interferences of one person's interests with the interests of another person, where potential bias may occur due to prior or existing personal or professional relationships.



- D. **Deciding Official** means the institutional official who makes final determinations on allegations of scientific misconduct and any responsive institutional actions. The Deciding Official will not be the same individual as the Research Integrity Officer and should have no direct prior involvement in the institution's inquiry, investigation, or allegation assessment.
- E. **Good faith allegation** means an allegation made with the honest belief that scientific misconduct may have occurred. An allegation is not in good faith if it is made with reckless disregard for or willful ignorance of facts that would disprove the allegations.
- F. **Inquiry** means gathering information and initial fact-finding to determine whether an allegation or apparent instance of scientific misconduct warrants an investigation.
- G. **Investigation** means the formal examination and evaluation of all relevant facts to determine if misconduct has occurred, and if so, to determine the responsible person and the seriousness of the misconduct.
- H. **ORI** means the Office of Research Integrity, the office within the U.S. Department of Health and Human Services (DHHS) that is responsible for the scientific misconduct and research integrity activities of the U.S. PHS.
- I. **PHS** means the U.S. Public Health Service, an operating component of the DHHS.
- J. **PHS regulation** means the PHS regulation establishing standards for institutional inquiries and investigations into allegations of scientific misconduct, which is set forth at 42 C.F.R. Part 50, Subpart A, entitled "A Responsibility of PHS Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science".
- K. **PHS support** means PHS grants, contracts, or cooperative agreements or applications therefore.
- L. **TS Alliance support** means TS Alliance grants, fellowships, or contracts, or a Letter of Intent or grant application submitted to the TS Alliance.
- M. **Research Integrity Officer** means the institutional official responsible for assessing allegations of scientific misconduct and determining when such allegations warrant inquiries and for overseeing inquiries and investigations and/or working closely with the Research Integrity Office of another institution that employs a TS Alliance-funded researcher. The TS Alliance Vice President and Director of Science will serve as the Research Integrity Officer.
- N. **Research record** means data, document, computer file, computer diskette, or any other written or non-written account or object that reasonably may be expected to provide evidence or information regarding the proposed, conducted, or reported research that constitutes the subject of an allegation of scientific misconduct. A research record includes, but is not limited to, Letter of Intent, grant or contract applications, whether funded or unfunded; grant or contract progress and other reports; laboratory notebooks; notes; correspondence; videos; photographs; X-ray film; slides; biological materials; computer files and printouts; manuscripts and publications; equipment use logs; laboratory procurement records; animal facility records; human and animal subject protocols; consent forms; medical charts; and patient research files.



- O. **Respondent** means the person against whom an allegation of scientific misconduct is directed or the person whose actions are the subject of the inquiry or investigation. There can be more than one respondent in any inquiry or investigation.
- P. **Retaliation** means any action that adversely affects the employment or other institutional status of an individual that is taken by an institution or an employee because the individual has in good faith, made an allegation of scientific misconduct or of inadequate institutional response thereto or has cooperated in good faith with an investigation of such allegation.
- Q. **Scientific misconduct or misconduct in science** means fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. It does not include honest error or honest differences in interpretations or judgments of data.

III. Rights and Responsibilities

- A. **Research Integrity Officer:** The Chief Executive Officer will appoint the Research Integrity Officer, who will have primary responsibility for implementation of the procedures set forth for investigations of allegations of scientific misconduct. The Research Integrity Officer will usually be, unless there is a conflict of interest, the Vice President and Director of Science. This individual should be well qualified to handle the procedural requirements involved and is sensitive to the varied demands made on those who conduct research, those who are accused of misconduct, and those who report apparent misconduct in good faith.

The Research Integrity Officer will appoint the inquiry and investigation committees and ensure that necessary and appropriate expertise is secured to carry out a thorough and authoritative evaluation of the relevant evidence in an inquiry or investigation. The Research Integrity Officer will attempt to ensure that confidentiality is maintained. When an inquiry or investigation is carried out by the institution that employs the respondent, the Research Integrity Officer will work closely with the Research Integrity Officer from that institution to ensure that a thorough and authoritative evaluation is conducted, and that confidentiality is maintained.

The Research Integrity Officer will assist inquiry and investigation committees and all institutional personnel in complying with these procedures and with applicable standards imposed by government or external funding sources. The Research Integrity Officer is also responsible for maintaining files of all documents and evidence and for the confidentiality and the security of the files.



The Research Integrity Officer will report to the TS Alliance Executive Committee and will keep them apprised of any developments during the course of the inquiry or investigation that may affect current or potential TS Alliance funding for the individual(s) under investigation or that TS Alliance needs to know to ensure appropriate use of TS Alliance funds and otherwise protect the public interest.

B. Complainant: The complainant will have an opportunity to testify before the inquiry and investigation committees, to review portions of the inquiry and investigation reports pertinent to his or her allegations or testimony, to be informed of the results of the inquiry and investigation, and to be protected from retaliation. Also, if the Research Integrity Officer has determined that the complainant may be able to provide pertinent information on any portions of the draft report, these portions will be given to the complainant for comment. The complainant is responsible for making allegations in good faith, maintaining confidentiality, and cooperating with an inquiry or investigation.

C. Respondent: The respondent will be informed of the allegations when an inquiry is opened and notified in writing of the final determinations and resulting actions. The respondent will also have the opportunity to be interviewed by and present evidence to the inquiry and investigation committees, to review the draft inquiry and investigation reports, and to have the advice of counsel.

The respondent is responsible for maintaining confidentiality and cooperating with the conduct of an inquiry or investigation. If the respondent is not found guilty of scientific misconduct, he or she has the right to receive institutional assistance in restoring his or her reputation.

D. Deciding Official: The Deciding Official will receive the inquiry and/or investigative report and any written comments made by the respondent or the complainant on the draft report. The Deciding Officer will consult with the Research Integrity Officer or other appropriate officials and will determine whether to conduct an investigation, whether misconduct occurred, whether to impose sanctions, or whether to take other appropriate administrative actions.



IV. General Policies and Principles

- A. Responsibility to Report Misconduct:** All employees or individuals associated with the TS Alliance should report observed, suspected, or apparent misconduct in science to the Research Integrity Officer. If an individual is unsure whether a suspected incident falls within the definition of scientific misconduct, he or she may call the Research Integrity Officer at the TS Alliance to discuss the suspected misconduct informally. Individuals working at an institution may also contact that institution's Research Integrity Officer to discuss potential allegations on an informal basis. If the circumstances described by the individual do not meet the definition of scientific misconduct, the Research Integrity Officer will refer the individual or allegation to the appropriate institutional office for resolution of the problem. At any time, an individual may have confidential discussions and consultations about concerns of possible misconduct with the Research Integrity Officer of the TS Alliance or of their institution and will be counseled about appropriate procedures for reporting allegations.
- D. Protecting the Complainant:** The Research Integrity Officer will monitor the treatment of individuals who bring allegations of misconduct or of inadequate institutional response thereto, and those who cooperate in inquiries or investigations. The Research Integrity Officer will ensure that these persons will not be retaliated against in terms and conditions of their employment or other status at their institution and will review instances of alleged retaliation for appropriate action.

Individuals should immediately report any alleged or apparent retaliation to the Research Integrity Officer of TS Alliance or of the institution where they are employed.

Also the TS Alliance and the institution will protect the privacy of those who report misconduct in good faith to the maximum extent possible. For example, if the complainant requests anonymity, the TS Alliance and the institution will make an effort to honor the request during the allegation assessment or inquiry within applicable policies and regulations and state and local laws, if any. The complainant will be advised that if the matter is referred to an investigation committee and the complainant's testimony is required, anonymity may no longer be guaranteed. Institutions are required to undertake diligent efforts to protect the positions and reputations of those persons who, in good faith, make allegations.



- E. Protecting the Respondent:** Inquiries and investigations will be conducted in a manner that will ensure fair treatment to the respondent(s) in the inquiry or investigation and confidentiality to the extent possible without compromising public health and safety or thoroughly carrying out the inquiry or investigation.

The TS Alliance or institutional employees accused of scientific misconduct may consult with legal counsel or a non-lawyer personal adviser (who is not a principal or witness in the case) to seek advice and may bring the counsel or personal adviser to interviews or meetings on the case. Note: Some institutions do not permit the presence of lawyers at interviews or meetings with institutional officials.

- F. Cooperation with Inquiries and Investigations:** The TS Alliance and institutional employees will cooperate with the Research Integrity Officers from both the TS Alliance and the institution in the review of allegations and the conduct of inquiries and investigations. Individuals have an obligation to provide relevant evidence to the Research Integrity Officers on misconduct allegations.

- G. Preliminary Assessment of Allegations:** Upon receiving an allegation of scientific misconduct, the Research Integrity Officer will immediately assess the allegation to determine whether there is sufficient evidence to warrant an inquiry, whether TS Alliance support or TS Alliance applications for funding are involved, and whether the allegation falls under the TS Alliance definition of scientific misconduct.

V. Conducting the Inquiry

- A. Initiation and Purpose of the Inquiry:** Following the preliminary assessment, if the TS Alliance and institutional Research Integrity Officer determine that the allegation provides sufficient information to allow specific follow-up, involves TS Alliance support, and/or falls under the TS Alliance definition of scientific misconduct, he or she will immediately initiate the inquiry process. In initiating the inquiry, the Research Integrity Officer should identify clearly the original allegation and any related issues that should be evaluated. The purpose of the inquiry is to make a preliminary evaluation of the available evidence and testimony of the respondent, complainant, and key witnesses to determine whether there is sufficient evidence of possible scientific misconduct to warrant an investigation. The purpose of the inquiry is not to reach a final conclusion about whether misconduct definitely occurred or who has responsible. The findings of the inquiry must be set forth in an inquiry report.



- B. Sequestration of Research Records:** After determining that an allegation falls within the definition of misconduct in science and involves the TS Alliance, the Research Integrity Officer must ensure that all original research records and materials and/or applications relevant to the allegation are immediately secured. The TS Alliance Research Integrity Officer may consult with the Research Integrity Officer at the institution which employs the respondent for advice and assistance in this regard.
- C. Appointment of the Inquiry Committee:** The Research Integrity Officer, in consultation with other institutional officials as appropriate, will appoint an inquiry committee of at least three individuals, and will appoint a committee chair as soon as possible (preferably within 14 days). The inquiry committee should consist of individuals who do not have real or apparent conflicts of interest in the case, are unbiased, and have the necessary expertise to evaluate the evidence and issues related to the allegation, interview the principals and key witnesses, and conduct the inquiry. These individuals may be scientists, clinicians, subject matter experts, administrators, lawyers, or other qualified persons, and they may be from TS Alliance's staff, volunteers, Board of Directors, Scientific Advisory Board or Professional Advisory Board, from within the institution which employs the respondent, or outside both the TS Alliance and the institution.

The Research Integrity Officer will notify the respondent of the proposed committee members as soon as they are appointed. The respondent may submit a written objection to any appointed member of the inquiry committee or expert based on bias or conflict of interest within 14 days. The objection should explain in detail why the individual should not be appointed to the inquiry committee. The Research Integrity Officer will replace the challenged member or expert with a qualified substitute if the objection is found to be valid.

- D. Committee and the First Meeting:** The Research Integrity Officer will prepare a charge for the inquiry committee that describes the allegations and any related issues identified during the allegation assessment and states that the purpose of the inquiry is to make a preliminary evaluation of the evidence and testimony of the respondent, complainant, and key witnesses to determine whether there is sufficient evidence of possible scientific misconduct to warrant an investigation as required by the TS Alliance. The purpose is not to determine whether scientific misconduct definitely occurred or who was responsible.

At the committee's first meeting, the Research Integrity Officer will review the charge with the committee, discuss the allegations, any related issues, and the appropriate procedures for conducting the inquiry, assist the committee with organizing plans for the inquiry, and answer any questions raised by the committee. The Research Integrity Officer, TS Alliance



counsel, and the institution's Research Integrity Officer and their institutional counsel will be present or available throughout the inquiry to advise the committee as needed.

- E. Inquiry Process:** The inquiry committee will normally interview the complainant, the respondent, and key witnesses as well as examine relevant research records, materials, and any other related materials. Then the inquiry committee will evaluate the evidence and testimony obtained during the inquiry. After consultation with the Research Integrity Officer and counsel (if needed), the committee members will decide whether there is sufficient evidence of possible scientific misconduct to recommend further investigation. The scope of the inquiry does not include deciding whether misconduct occurred or conducting exhaustive interviews and analyses.

VI. The Inquiry Report

- C. Elements of the Inquiry Report:** A written inquiry report must be prepared that states the name and title of the committee members and experts, if any; the allegations; the TS Alliance support; a summary of the inquiry process used; a list of research records reviewed; summaries of any interviews; a description of the evidence in sufficient detail to demonstrate whether an investigation is warranted or not; and the committee's determination as to whether an investigation is recommended and whether any other actions would be taken if an investigation is not recommended. Counsel will review the report for legal sufficiency.
- D. Comments on the Draft Report by the Respondent and the Complainant:** The Research Integrity Officer will provide the respondent with a copy of the draft inquiry report for comment and rebuttal and will provide the complainant, if he or she is identifiable, with portions of the draft inquiry report that addresses the complainant's role and opinions in the investigation. Note: The Research Integrity Officer may provide the complainant with a summary of the inquiry findings for comment instead of portions of the draft report if so desired.
 - 1. Confidentiality:** The Research Integrity Officer may establish reasonable conditions for review to protect the confidentiality of the draft report.
 - 2. Receipt of Comments:** Within 14 calendar days of their receipt of the draft report, the complainant and respondent will provide their comments, if any, to the inquiry committee. Any comments that the complainant or respondent submits on the draft report will become part of the final inquiry report and record. Based on the comments, the inquiry committee may revise the report as appropriate.

C. Inquiry Decision and Notification:

- 1. Decision by Deciding Official:** The Research Integrity Officer will transmit the final report and any comments to the Deciding Official, who will make the determination of whether findings from the inquiry provide sufficient evidence of possible scientific misconduct to justify conducting an investigation. The inquiry is completed when the Deciding Official makes this determination, which will be made within 14 days of receiving the inquiry report. Any extension of this period will be based on good cause and recorded in the inquiry file.
- 2. Notification:** The Research Integrity Officer will notify both the respondent and the complainant in writing of the Deciding Official's decision of whether to proceed to an investigation and will remind them of their obligation to cooperate in the event an investigation is opened. The Research Integrity Officer will also notify all appropriate institutional officials of the Deciding Official's decision.
- 3. Restoration of Reputation:** The TS Alliance will undertake diligent efforts, as appropriate, to restore the reputation of persons alleged to have engaged in misconduct when allegations of such misconduct are not confirmed.

- D. Time Limit for Completing the Inquiry Report:** The inquiry committee will normally complete the inquiry and submit its report in writing to the Research Integrity Officer no more than 60 calendar days following its first meeting, unless the Research Integrity Officer approves an extension for good cause. If the Research Integrity Officer approves an extension, the reason for the extension will be entered into the records of the case and the report. The respondent will also be notified of the extension.

VII. Conducting the Investigation

- A. Purpose of the Investigation:** The purpose of the investigation is to explore in detail the allegations, to examine the evidence in depth, and to determine specifically whether misconduct has been committed, by whom, and to what extent. The investigation will also determine whether there are additional instances of possible misconduct that would justify broadening the scope beyond the initial allegations. This is particularly important where the alleged misconduct involves clinical trials or potential harm to human subjects or the general public or if it affects research that forms the basis for public policy, clinical practice, or public health practice. The findings of the investigations will be set forth in an investigation report.
- B. Sequestration of the Research Records:** The Research Integrity Officer will immediately sequester any additional pertinent research records that were not previously sequestered during the inquiry. This sequestration should occur before or at the time the respondent is notified that an investigation has begun. The need for additional sequestration of records may occur for any number of reasons, including the institution's or the TS Alliance's decision to investigate additional allegations not considered during the inquiry stage or the identification of records during the inquiry process that has not been previously secured. The procedures to be followed for sequestration during the investigation are the same procedures that apply during the inquiry.

- C. Appointment of the Investigation Committee:** The Research Integrity Officer, in conjunction with other TS Alliance officials as appropriate, will appoint an investigation committee and the committee chair within 14 days of the notification to the respondent that an investigation is planned or as soon thereafter as practicable. The investigation committee should consist of at least three individuals who do not have real or apparent conflicts of interest in the case, are unbiased, and have the necessary expertise to evaluate the evidence and issues related to the allegations, interview the principals and key witnesses, and conduct the investigation. These individuals may be scientists, clinicians, administrators, subject matter experts, lawyers, or other qualified persons, and they may be from inside or outside TS Alliance. Individuals appointed to the investigation committee may also have served on the inquiry committee.

The Research Integrity Officer will notify the respondent of the proposed committee membership within 14 days. The respondent may submit a written objection to the Research Integrity Officer to any appointed member of the investigation committee or expert. The Research Integrity Officer will determine whether to replace the challenged member or expert with a qualified substitute.

D. Charge to the Investigation Committee and the First Meeting:

- 1. Charge to the Committee:** The Research Integrity Officer will define the subject matter of the investigations in a written charge to the committee that describes the allegations and related issues identified during the inquiry, defines scientific misconduct, and identifies the name of the respondent. The charge will state that the committee is to evaluate the evidence and testimony of the respondent, complainant, and key witnesses to determine whether, based on a preponderance of the evidence, scientific misconduct occurred and, if so, to what extent it occurred, who was responsible, and its seriousness.
- 2.** During the investigation, if any additional information becomes available that substantially changes the subject matter of the investigation or would suggest additional respondents, the committee will notify the Research Integrity Officer, who will determine whether it is necessary to notify the respondent of the new subject matter or to provide notice to additional respondents.
- 3. The First Meeting:** The Research Integrity Officer, with the assistance of counsel (if needed), will convene the first meeting of the investigation committee to review the charge, the inquiry report, and the prescribed procedures and standards for the conduct of the investigation, including the necessity for confidentiality and for developing a specific investigation plan. The investigation committee will be provided with a copy of these instructions and, where TS Alliance funding is involved, the TS Alliance regulation.

- E. Investigation Process:** The investigation committee will be appointed and the process initiated within 60 days of the completion of the inquiry, if findings from that inquiry provide a sufficient basis for conducting an investigation. The investigation will normally involve examination of all documentation including, but not necessarily limited to, relevant research records, computer files, proposals, grant applications, Letter of Intent, manuscripts, publications, correspondence, memoranda, e-mail correspondence and/or notes of telephone calls. Whenever possible, the committee should interview the complainant(s), the respondent(s), and other individuals, who might have information regarding aspects of the allegations. Interviews of the respondent should be tape recorded or transcribed. All other interviews should be transcribed, tape recorded, or summarized. Summaries or transcripts of the interviews would be prepared, provided to the interviewed party for comment or revision, and included as part of the investigatory file.

VIII. THE INVESTIGATION REPORT

- A. Elements of the Investigation Report:** The final report submitted to the TS Alliance Executive Committee and the ORI (if PHS funding is involved) must describe the policies and procedures under which the investigation was conducted, describe how and from whom information relevant to the investigation was obtained, states the findings, and explains the basis for the findings. The report will include the actual text or an accurate summary of the views of any individual(s) found to have engaged in misconduct as well as a description of any sanctions imposed and administrative actions taken by the TS Alliance.
- B. Comments on the Draft Report:**
- 1. Respondent:** The Research Integrity Officer will provide the respondent with a copy of the draft investigation report for comment and rebuttal. The respondent will be allowed 14 calendar days to review and comment on the draft report. The respondent's comments will be attached to the final report. The findings of the final report would take into account the respondent's comments in addition to all the other evidence.
 - 2. Complainant:** The Research Integrity Officer will provide the complainant, if he or she is identifiable, with those portions of the draft investigation report that address the complainant's role and opinions in the investigation. The report should be modified, as appropriate, based on the complainant's comments.
 - 3. TS Alliance Counsel:** The draft investigation report will be transmitted to the TS Alliance counsel for review. Comments and/or edits should be incorporated into the report as appropriate.

4. **Confidentiality:** In distributing the draft report, or portions thereof, to the respondent and complainant, the Research Integrity Officer will inform the recipient of the confidentiality under which the draft report is made available and may establish reasonable conditions to ensure such confidentiality. For example, the Research Integrity Officer may request the recipient to sign a confidentiality statement or to come to his or her office to review the report.

- C. **Institutional Review and Decision:** Based on a preponderance of the evidence, the Deciding Official will make the final determination whether to accept the investigation report, its findings, and the recommended institutional actions. If this determination varies from that of the investigation committee, the Deciding Official will explain in detail the basis for rendering a decision different from that of the investigation committee in the TS Alliance's letter transmitting the report to the TS Alliance Executive Committee. The Deciding Official's explanation should be consistent with the TS Alliance definition of scientific misconduct, TS Alliance's policies and procedures, and the evidence reviewed and analyzed by the investigation committee. The Deciding Official may also return the report to the investigation committee with a request for further fact-finding or analysis. The Deciding Official's determination, together with the investigation committee's report, constitutes the final investigation report for purposes of the TS Alliance review.

When a final decision on the case has been reached, the Research Integrity Officer will notify both the respondent and the complainants in writing. In addition, the Deciding Official will determine whether law enforcement agencies, professional societies, professional licensing boards, editors of journals in which falsified reports may have been published, collaborators of the respondent in the work, or other relevant parties should be notified of the outcome of the case. The Research Integrity Officer is responsible for ensuring compliance with all notification requirements of other funding or sponsoring agencies and the TS Alliance.

- D. **Transmittal of the Final Investigation Report to the TS Alliance Executive Committee:** After comments have been received and the necessary changes have been made to the draft report, the investigation committee should transmit the final report with attachments, including the respondent's and complainant's comments, will be transmitted to the Executive Committee by the Deciding Official.
- E. **Time Limit for Completing the Investigation Report:** An investigation should ordinarily be completed within 120 days of its initiation, with the initiation being defined as the first meeting of the investigation committee. This includes conducting the investigation, preparing the report of findings, making the draft report available to the subject of the investigation for comment, submitting the report to the Deciding Official for approval, and submitting the report to the TS Alliance Executive Committee.



IX. Requirements for Reporting to the TS Alliance and the Office of Research Integrity (ORI)

- A.** The decision to initiate an investigation must be reported in writing to the TS Alliance Chief Executive Officer, as well as the ORI (if PHS funding is involved) on or before the date that the investigation begins. At a minimum, the notification should include the name of the person(s) against whom the allegations have been made, the general nature of the allegation as it relates to the TS Alliance definition of scientific misconduct, and the TS Alliance applications or grant number(s) involved. The TS Alliance Executive Committee and ORI must also be notified of the final outcome of the investigation and must be provided with a copy of the investigation report. Any significant variations from the provisions of the policies and procedures should be explained in any reports submitted to the TS Alliance Executive Committee and the ORI. The TS Alliance Executive Committee and/or the Deciding Official will provide a final report to the TS Alliance Board of Directors on all actions taken.
- B.** If for any reason the inquiry or investigation is terminated without completing all relevant requirements, the Research Integrity Officer will submit a report of the planned termination to the TS Alliance Executive Committee and to the ORI (if necessary), including a description of the reasons for the proposed termination.
- C.** The TS Alliance will promptly advise ORI of any developments during the course of the investigation which disclose the facts that may affect current or potential DHHS funding for individual(s) under investigation or that the PHS needs to know to ensure appropriate use of Federal funds and to otherwise protect the public interest.
- D.** If it is determined that it will not be possible to complete the investigation in 120 days, the Research Integrity Officer will submit to the TS Alliance Executive Committee a written request for an extension that explains the delay, reports on the progress to date, estimates the date of completion of the report, and describes other necessary steps to be taken. If the request is granted, the Research Integrity Officer will file periodic progress reports as requested by the TS Alliance Executive Committee. In addition, the TS Alliance will submit to the ORI a request for an extension if unable to complete the investigation in 120 days (if necessary). The extension request to the ORI will include an explanation for the delay, an interim report on the progress to date, an outline of what remains to be done, and an estimated date of completion.
- E.** When TS Alliance funding or applications for funding are involved and an admission of scientific misconduct is made, the Research Integrity Officer will contact the TS Alliance Executive Committee for consultation and advice. Normally, the individual making the admission will be asked to sign a statement attesting to the occurrence and extent of misconduct. When the case involves TS Alliance funds, the institution where that individual is employed cannot accept an admission of scientific misconduct as a basis for closing a case or not undertaking an investigation without prior approval of the TS Alliance Executive Committee.

- F.** The Research Integrity Officer will notify the proper officials at the institution, as well as the Office of Research Integrity at the PHS (if necessary) at any stage of the inquiry or investigation if:
1. there is an immediate health hazard involved;
 2. there is an immediate need to protect Federal or TS Alliance funds and/or equipment;
 3. there is an immediate need to protect the interests of the person(s) making the allegations or of the individual(s) who is the subject of the allegations as well as his or her co-investigators and associates, if any;
 4. it is probable that the alleged incident is going to be reported publicly; or
 5. the allegation involves a public health sensitive issue, e.g., a clinical trial; or
 6. there is a reasonable indication of possible criminal violation. In this instance, the institution must inform TS Alliance and PHS within 24 hours of obtaining that information.

X. TS Alliance Administrative Actions

The TS Alliance will take appropriate administrative actions against individuals when an allegation of misconduct has been substantiated.

If the Deciding Official determines that the alleged misconduct is substantiated by the findings, he or she will decide the appropriate actions to be taken, after consultation with the Research Integrity Officer. The actions may include and or all of the following, or other actions as deemed necessary:

1. withdrawal or correction of all pending or published abstracts and papers emanating from the research where scientific misconduct was found;
2. removal of the responsible person from the particular project, letter of reprimand, or special monitoring of future work on that project;
3. prohibition of the responsible person(s) from any future grant applications to the TS Alliance; and/or
4. restitution of funds as appropriate.

XI. Other Considerations

- A. Termination of Employment or Resignation Prior to Completing Inquiry or Investigation:** The termination of the respondent's employment, by resignation or otherwise, before or after an allegation of possible scientific misconduct has been reported, will not preclude or terminate the misconduct procedures.

If the respondent, without admitting to the misconduct, elects to resign his or her position prior to the initiation of an inquiry, but after an allegation has been reported, or during an inquiry or investigation, the inquiry or investigation will proceed. If the respondent refuses to participate in the process after resignation, the committee will use its best efforts to reach a conclusion concerning the allegations, noting in its report the respondent's failure to cooperate and its effect on the committee's review of all the evidence.

- B. Restoration of the Respondent's Reputation:** If no misconduct is found and the TS Alliance Executive Committee concurs, the Research Integrity Officer will consult with the respondent and undertake reasonable efforts to restore the respondent's reputation. Depending on the particular circumstances, the Research Integrity Officer should consider notifying those individuals aware of or involved in the investigation of the final outcome, publicizing the final outcome in forums in which the allegation of scientific misconduct was previously publicized, or expunging all reference to the scientific allegation from the respondent's file. The institution where the respondent is employed should also do everything possible to assist in the restoration of the respondent's reputation.
- C. Protection of the Complainant and Others:** Regardless of whether it is determined that scientific misconduct occurred, the Research Integrity Officer will undertake reasonable efforts to protect complainants who made allegations of scientific misconduct in good faith and others who cooperate in good faith with inquiries and investigations of such allegations. Upon completion of an investigation, the Deciding Official will determine, after consulting with the complainant, what steps, if any, are needed to restore the position or reputation of the complainant. The Research Integrity Officer is responsible for implementing any steps the Deciding Official approves. The Research Integrity Officer will also take appropriate steps during the inquiry and investigation to prevent any retaliation against the complainant.
- D. Allegations Not Made in Good Faith:** If relevant, the Deciding Official will determine whether the complainant's allegations of scientific misconduct were made in good faith. If an allegation was not made in good faith, the Deciding Official will determine whether any administrative action should be taken against the complainant.
- E. Interim Administrative Actions:** TS Alliance officials will take interim administrative actions, as appropriate, to protect TS Alliance funds and ensure that the purposes of the TS Alliance financial assistance are carried out.



XII. Record Retention

After completion of a case and all ensuing related actions, the Research Integrity Officer will prepare a complete file, including the records of any inquiry or investigation and copies of all documents and other materials furnished to the Research Integrity Officer or committees. The Research Integrity Officer will keep the file for three years after completion of the case to permit later assessment of the case. This documentation will be made available to the Director of the ORI at NIH (if PHS funds are involved). Only individuals associated with TS Alliance who are authorized by the Deciding Official and the Research Integrity Officer will be given access to the records upon request.

Approved by TS Alliance Board of Directors: September 17, 1995.

Revisions approved June 1, 1996.

Revised policy approved by the Science & Medical Committee: May 17, 2006.

Approved by TS Alliance Board of Directors: June 21, 2006.

Appendix F – Scientific Misconduct Policy



Appendix G

INTELLECTUAL PROPERTY POLICY

Though the primary focus of the Tuberous Sclerosis Alliance (hereinafter designated TS Alliance) in funding scientifically meritorious research on tuberous sclerosis complex (TSC) is to advance its mission of finding a cure for TSC while improving the lives of those affected, the TS Alliance recognizes that potentially patentable inventions or other intellectual properties (hereinafter called the "Properties") having public health, scientific, business or commercial application or value may be made in the course of research supported by the TS Alliance. It is the desire of the TS Alliance that such Properties be administered in such a manner that they are brought into public use at the earliest possible time. The TS Alliance recognizes that this may be best accomplished by protecting and licensing proprietary rights in the Properties.

The TS Alliance is a not-for-profit organization supported by public contributions that has used these contributions to support scientific research on TSC since 1984. The TS Alliance believes that it has a responsibility to adopt policies that will insure that potentially beneficial discoveries and Properties resulting from scientific research funded in whole or in part by the TS Alliance are developed, are brought to practical application and are made available to the public.

1. This Intellectual Property Policy will be adhered to by, and is binding on, all Grantee Institutions and Awardees (hereinafter, collectively "Grantees" and individually "Grantee"). Acceptance of the grant award from the TS Alliance constitutes acceptance of the terms and conditions of this Policy.
2. The Grantee institution shall notify the TS Alliance at the earliest time possible, but not later than one week after filing a patent application or upon entering into negotiations with a potential licensee, whichever event occurs first, of all potentially patentable or other intellectual properties that result from support in whole or in part from grant awards from the TS Alliance. In addition, the Grantee shall at the same time notify the TS Alliance whether it intends to pursue a patent for the Properties. The Grantee shall notify the TS Alliance in writing after filing an application for a patent. The Grantee shall also notify the TS Alliance in writing after receipt of any patent.

The TS Alliance agrees to keep all information provided by the Grantee and/or Grantee institution confidential and not to release any information relating to such inventions, intellectual property or applications for protection to any third party, except as specifically set forth below. All patenting expenses or costs associated with the protection of other intellectual property shall be borne solely by the Grantee institution.

3. The TS Alliance will defer to the established written intellectual properties policy of the Grantee or any not-for-profit institution for which an individual awardee works provided that a copy of the established written policy has been provided to the TS Alliance, and that such policy is not inconsistent with the purposes, goals and mission of the TS Alliance. The patent or patent application shall not be abandoned without notifying TS Alliance in writing and permitting it to identify another institution or entity who will



license the Property. With such notification of Grantee's intent to abandon, Grantee will also inform TS Alliance if it has a legal obligation to relinquish rights in the patent application to the government or to the inventor(s). If Grantee has an obligation to relinquish rights in the patent application to the government or to the inventor(s), Grantee will inform the TS Alliance in writing if neither the government nor inventor(s) elect to proceed. If the Grantee has no such obligation, the TS Alliance, at its sole discretion, may elect to proceed with prosecution of the patent application. Once the TS Alliance is informed in writing that there is no such obligation or such obligation has been refused by the government and/or inventor(s), the TS Alliance will inform Grantee within 20 business days of its intent to proceed with continued prosecution. The TS Alliance will pay all costs and fees related to the continued prosecution if the TS Alliance elects to proceed, and Grantee agrees to assign all patent rights to the TS Alliance or to provide to the TS Alliance a worldwide, exclusive, royalty-free license with an unlimited right to sublicense, at TS Alliance's sole discretion.

Approved by Research and Education Committee: April 17, 1995

Revisions Approved by Research and Education Committee: August 14, 1995

Approved by the Board of Directors with revisions: September 17, 1995

Revisions approved by the Science & Medical Committee: August 16, 2006

Approved by the Board of Directors: (pending)

Tuberous Sclerosis Complex (TSC) National Database (DB)
Annual Report – W81XH-04-0896
PI: Dr. Steven Sparagana

Appendix T – Recruitment Brochure (Draft version)

What is the TS Alliance?

The TS Alliance is dedicated to finding a cure for TSC while improving the lives of those affected. Founded in 1974, the TS Alliance was established by four mothers who sought to provide fellowship, generate awareness and provide hope to those that share the common bond of TSC.

For more than 30 years, the TS Alliance has been a leading resource for individuals, families and health care providers, helping to improve care and providing referrals to experienced specialists for those affected with TSC. In addition to supporting TSC research, the TS Alliance provides printed materials for families and physicians seeking the most current and thorough information on TSC.



For More Information

Contact the TS Alliance at 1-800-225-6872 or
E-mail: info@tsalliance.org

Contact your local TSC Clinic listed below.

Funding to support the development of the TSC Natural History Database was provided by the Tuberous Sclerosis Alliance and a Natural History Development Award to Steven Sparagana, M.D. from the Tuberous Sclerosis Complex Research Program in the Congressionally Directed Medical Research Program, Department of Defense.



801 Roeder Road, Suite 750
Silver Spring, MD 20910
www.tsalliance.org

Tuberous Sclerosis Complex Natural History Database Project

*The Tuberous Sclerosis Alliance
seeks individuals with
tuberous sclerosis complex (TSC)
to participate in a nationwide
research project to
learn more about how
TSC affects individuals
throughout their lives.*



What is the TSC Natural History Database Project?

This information-collecting project is sponsored by the Tuberous Sclerosis Alliance (TS Alliance) and conducted through a network of TSC Clinics nationwide. The TS Alliance and the TSC Clinics invite

individuals with tuberous sclerosis complex (TSC) to participate in the first-ever effort to collect and store medical information about them over their lifetimes.



The information about you and hundreds of others with TSC who volunteer for this project will help TSC researchers to:

- Better understand how the disease affects individuals at different times in their lives.
- Perform research studies using the collected information.
- Find new ways to treat individuals with TSC.
- Identify appropriate persons with TSC to participate in other research studies.

Who can volunteer for this project?

Males and females of any age or race who have TSC may volunteer for the project through any of the participating TSC Clinics.



What does participation involve?

If you volunteer for this research project, information about you will be collected when you visit the TSC Clinic.

Your permission to use medical information from other doctors you see now or saw in the past will also be obtained. Your medical information will be collected and stored in a secure, web-based computer system for TSC researchers to use. You can change your mind at any time about participating. Your decision will not affect your relationship with your doctor or the TSC Clinic. You will not receive any form of payment or special care if you volunteer for the project.



Why should you participate in this project?

Project participants will:

- Gain access to new research studies for persons with TSC.
- Help others by providing information for TSC researchers to learn more about how TSC affects various organs in the human body.

There are no medical risks for participation in the TSC Natural History Database project because it is a non-treatment study. This means any tests or procedures performed by your physicians, or any drugs you receive, will be part of your standard medical care.

Human research studies are reviewed and approved by an Institutional Review Board (i.e. a committee of experts and non-experts) to



make sure that the rights of people who volunteer to participate in the studies are protected. The TSC Natural History Database Project will follow a protocol – a study plan that details what researchers will do in the study. As the TSC Natural History Database Project enrolls more and more individuals with TSC, researchers will report the Database Project results at scientific meetings and to medical journals. Individual participants' names will remain secret and will never be mentioned in these reports. Your name, address, medical record number, and social security number will not be entered into the database. The research team at the TSC Clinic where you enroll in the study will be able to identify you and your medical records and make the link to your unique code in the database. The TS Alliance TSC Natural History Database Project Administrator will also view records that may contain your name in order to make sure that you willingly volunteered to participate in this project (i.e. Informed Consent) and that the information collected in the database is correct.

Tuberous Sclerosis Complex (TSC) National Database (DB)
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PI: Dr. Steven Sparagana

Appendix U – Training Schedule



**TSC NATURAL HISTORY DATABASE PROJECT
TRAINING SESSION SCHEDULE**

SESSION	TOPIC	TIME COMMITMENT (APPROXIMATE)	KEY PERSONNEL
1	Data Viewing and Entry	2 hours	Clinic Director (PI), Clinic/Nurse Coordinator(s)* Data Entry Person
SHORT BREAK			
2	Generating Reports	30 minutes	Clinic Director (PI), Clinic/Nurse Coordinator(s)*
3	Administration – Users Access, Creating New Users	30 minutes	Clinic/Nurse Coordinator(s)*
LUNCH BREAK			
4	Practice	2 hours	Clinic/Nurse Coordinator(s)* Data Entry Person

***Mandatory Attendance**