Cardiac Amyloidosis Registry Study ("CARS")

Version: Amendment 5

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Contents

1.0 Summary of Changes

Affected Section(s)	Summary of Revisions Made	Rationale
Section 4.3 Total Number of Study Sites/Total Number of Subjects Projected	Number of collaborating sites has increased. The total number of participating sites is yet to be determined.	List of participating sites have been updated in appendix 1.
Appendix 1	Addition of participating sites to appendix 1.	Updated appendix 1 to include additional sites that have joined the registry.

Protocol Amendment 4 Changes

Affected Section(s)	Summary of Revisions Made	Rationale
Section 4.3 Total Number of Study Sites/Total Number of Subjects Projected	Added number of collaborating sites. The total number of participating sites is yet to be determined.	List of participating sites have been entered in appendix 1.
Section 5.2 Exclusion Criteria	For external sites, records that indicate No Research Flag or are noted as “Break the Glass” may be included based on institutional policies and appropriate approvals, as applicable.	Sites to follow local institutional policies based on “Break the Glass” records.
Appendix 1	Addition of participating sites to appendix 1.	Updated appendix 1 to include additional sites that have joined the registry.

Protocol Amendment 3 Changes

Affected Section(s)	Summary of Revisions Made	Rationale
Section 4.3 Total Number of Study Sites/Total Number of Subjects Projected	Added number of collaborating sites. The total number of participating sites is yet to be determined.	List of participating sites have been entered in appendix 1.
Section 6.2 Confidentiality of Data	Registration of study in ClinicalTrials.gov	Registration of this observational study in ClinicalTrials.gov for publication purposes.
Throughout Protocol	Changing de-identified to limited data set	Edits made to clarify that the data captured and entered in redcap will include identifiers.
Appendix 1	Addition of appendix 1.	Appendix 1 added to list all participating sites as this is a multi-center registry.

2.0 Background, Rationale

Amyloidosis is a rare, multisystem disorder in which normally soluble protein is deposited in tissues, leading to organ dysfunction. Several proteins have been identified to potentially lead to amyloid cardiomyopathy (AC). The most commonly encountered abnormal proteins are due to excess immunoglobulin light chain (AL) resulting from plasma cell dyscrasia in the bone marrow and transthyretin, a transport protein produced by the liver. Amyloidosis due to transthyretin typically occurs either as wild type (normal) transthyretin (ATTRwt) or mutant transthyretin (ATTRm) protein sequence. More than 120 mutations have been reported that lead to ATTRm with certain mutations having a propensity to lead to a predominant clinical phenotype of AC and others causing a predominantly neuropathic phenotype. ATTRwt (previously known as senile systemic amyloidosis) typically affects older male patients. ATTRm generally presents at an earlier age and is inherited in an autosomal dominant trait. Transthyretin is a 127 amino acid protein which circulates as a tetramer and carries the thyroid hormone thyroxine and retinol-binding protein bound to retinol. The pathogenicity of ATTR is related to the instability of the tetramers which exist in equilibrium with its constituent monomers. The monomers misfold to form prefibrillar proteins which then aggregate to form amyloid fibrils which deposit in various organs with a particular predilection for but not limited to, the heart and nervous system. The mechanisms of injury are not entirely understood. There are data to suggest that the pre-fibrillar protein aggregates may also directly contribute to organ toxicity. Light chain proteins seem to provoke direct oxidative stress

as well as apoptosis in cardiomyocytes. The deposition of misfolded proteins leads to stiff, non-compliant, myocardium and the extracellular space is expanded by deposits, causing myocardial hypertrophy and restrictive cardiomyopathy with diastolic abnormalities observed on echocardiography. Beyond diastolic abnormalities, atrial arrhythmias, pericardial and pleural effusions are frequently observed. In systemic amyloidosis, findings can include neuropathy, nephrotic syndrome, macroglossia, carpal tunnel syndrome, and bleeding, can be seen due to fibril deposition in various tissue beds.

The prognosis of patients with either AL or ATTR cardiomyopathy depends on the extent and severity of organ involvement although overall, untreated AL has a much more rapidly progressive course. Kumar et al reported on an updated prognostic staging system for patients with cardiac AL amyloidosis identifying three independent predictors of mortality: (1) the difference between involved and uninvolved light chains (2) cardiac troponin T, and (3) NT-proBNP. Overall survival significantly decreased for each additional biomarker above the cutoff values. This scoring system predates the use of proteasome inhibitors such as bortezomib and therefore limits its contemporary applicability. Beyond the use of biomarkers, the degree of late gadolinium enhancement seen on cardiac magnetic resonance has prognostic utility for long-term mortality in both AL and ATTR.

Median survival in a single-center study of patients with ATTRwt was 3.6 years with outcomes remaining static over the last 30-40 years. The authors report on three stages of disease based on whether cardiac biomarker values were above or below an NT-proBNP and/or troponin T cutoff. Four-year overall survival worsened with increasing stage. For ATTRm, untreated survival ranges between 2 and 15 years and dependent upon mutation sub-type. The V122I or valine to isoleucine mutation is the most common sub-type in the US and carries an 80% survival at 1 year and 28% at 5 years, respectively. Updated scoring systems and prognostication models will be necessary for AL and ATTR as novel therapies bend survival curves.

Rapezzi et al. reported that, of patients diagnosed with systemic amyloidosis, 51% of patients with AL and 34% of patients with TTR amyloid demonstrated evidence of cardiac amyloidosis, often with rapid progression to heart failure. Therefore, detailed characterization of AL and TTR cardiac amyloidosis and the development of effective treatment plans offering long-term survival for both diseases are of vital importance.

The recent availability of tafamidis for ATTR cardiomyopathy and patisiran and inotersen for hereditary ATTR neuropathy will affect outcomes in patients and the impact of these therapies will need to be assessed. Similarly, for AL amyloidosis, significant advances in chemotherapy and autologous stem cell transplantation have led to improved survival.

Patients with end-stage cardiac disease may however need to be considered for advanced therapies including mechanical circulatory support and heart transplantation.

Given the rare nature of these diseases, a large, multi-center effort to describe the characteristics of these patients and their outcomes with these novel treatment modalities has not been established. This multi-center effort will represent the largest collection of AL and TTR cardiac amyloidosis to date. (TBD) academic medical centers from the US will compile demographic, hemodynamic and organ-involvement data, as well as treatment strategies for AL and TTR amyloidosis.

3.0 Study Objectives

- Increase understanding of disease presentation, progression, and various treatment plans for AL and TTR cardiac amyloid through study of a large cohort of patients with AL and TTR amyloidosis.
- Identify demographic, hemodynamic, and organ-involvement data that are predictors of long-term survival.
- Compare the disease presentation, treatment strategies, and relative survival of AL and TTR amyloidosis patients, including patients listed for heart transplant.
- Compare the use of therapeutic treatment modalities and their effect on long-term survival.
- Compare the presentation and relative survival corresponding to different TTR mutations.
- Analysis of diagnostic procedures

  Note: as the study develops and the transfer of data shows to be successful, additional data points will be identified to support the objectives. Only data points consistent with the research objectives will be obtained.

4.0 Study Design and Procedures

4.1 Study Type

<u>At all sites</u>
This registry is an observational, multi-center study designed to collect data and analyze it retrospectively on patients with AL or TTR cardiac amyloidosis who have been evaluated and treated at major amyloid centers across the US and internationally between 1997 and 2025. Patients will be identified by the investigator and/or study team using established IRB-approved local databases. Where this is not available, subjects under the care of the local investigator will be identified and consented. No patient visits or patient procedures will be required for the purpose of this study. Data will be abstracted from the patients' medical records from the time of presentation through most recent follow-up.

At all sites (excluding Cedars-Sinai Medical Center) appropriate consent will be sought or justification for a waiver must be provided for the collection of data for purposes of

this registry. Sites are to obtain IRB approval through Western Institutional Review Board® (WIRB®) or through their local Institutional Review Board.

At Cedars-Sinai Medical Center (CSMC)

Cedars-Sinai data will include data that has been or will be collected under the Advanced Heart Disease registry (Pro00022311). The research activities at CSMC for this study directly fall under the consent obtained from subjects for inclusion in the Advanced Heart Disease registry. Therefore, consent for this study was obtained under a separate protocol at CSMC and all CSMC subjects provided consent to be included in this registry. As such, Western Institutional Review Board® (WIRB®) will not require consent for CSMC. Data from deceased individuals treated at CSMC will be included if appropriate consent was already obtained under the Advanced Heart Disease registry before their death.

Confidential REDCap data will be stored and transferred between the existing Advanced Heart Registry and the new Heart Amyloidosis Registry. Primary identifiers including dates (year of birth, gender, age at presentation) will be recorded; however, these identifying dates will be used only in analysis to report duration between events and will not be reported in raw form.

4.2 Date Range of Study

The study population will include all adults evaluated at CSMC and collaborating institutions between 1997 and 2025. Cases will be included from 1997 to 2025. Follow-up information through end of study will be included.

Data will be obtained from 1997 through 2025, meaning that some patients may be seen on an ongoing basis.

4.3 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at multiple sites in the United States and internationally. Currently there are 25 additional sites participating in the United States. The total number of collaborating sites is yet to be determined. The participating sites are listed in appendix 1. It is expected that the total patient population will be approximately 5,000 patients.

4.4 Record Review and Data/ Sources

Data that will be abstracted from the patients' medical records are listed on the attached document: Data Chart Extraction Variables. Patients will be identified by the investigator and/or study team using established IRB-approved local databases. Where this is not available, subjects under the care of the local investigator will be identified and consented. Access to local electronic medical records may be required and where necessary, local IRB approval will be obtained.

5.0 Eligibility/Subject Enrollment

5.1 Inclusion Criteria

- Males and Females ages 18+
- Established diagnosis of AL or TTR cardiomyopathy identified or treated within the timeframe
- Specific to CSMC: If the individual provided consent while they were alive for the Advanced Heart Disease registry (Pro00022311), and if sufficient information exists in their chart, their data will be included.
- Information on deceased individuals may be included, but only with the appropriate approval from the external site IRB and/or according to the federal regulations for the protection of human subjects.

5.2 Exclusion Criteria

- At Cedars-Sinai, records that specifically state not to be used in research will not be accessed. Patients who have enacted a No Research Flag or are noted as "Break the Glass" will not be included**. For external sites**, records that indicate No Research Flag or are noted as "Break the Glass" may be included based on institutional policies and appropriate approvals, as applicable.

6.0 Data Collection and Management

6.1 Data/ Storage

Following chart abstraction of patient data at each clinical center, a limited data set will be shared with Cedars-Sinai Medical Center, the project administrator, through secure data entry in the CSMC REDCap database built for the registry which has secure web authentication and Secure Sockets Layer (SSL) encryption. No identifiers will be included in data transferred from one institution to another. Lists linking identifiers to data will be maintained for each institution and will not be shared with external institutions or sites. Each institution will gain access to the approved REDCap project, hosted by Cedars-Sinai, after the collaboration agreement is fully executed and WIRB or local IRB approval is obtained.

Cedars-Sinai, acting as the project administrator, will maintain overall responsibility for database integrity. Each participating academic center will designate which members of their study team need access the Redcap study database for data entry purposes. Each participating center will submit their research proposals involving the registry data from all participating sites using the online proposal form provided by Cedars Sinai. All such research proposals will have to be reviewed and approved during scheduled or ad-hoc Investigator meetings. Prior to release of any publications

and or presentations, the manuscript or presentation would be distributed to the consortium for comments and or edits.

All compiled data (limited data set) will be kept in the REDCap database to allow for institution-specific updates to patient data and for the addition of new patients evaluated and or listed for transplant at each institution. Data will be collected and kept for 10 years following the establishment of the database. Upon study completion, the secured database will be digitally locked to new additions and will remain encrypted.

6.2 Confidentiality of Data

To ensure the safety and integrity of the data collected in the study, all data will be stored securely in a REDCap database to which only the principal investigator, co-investigators and study coordinators will have access. Data will be collected as a limited data set prior to entry into the RedCap database by local IRB approved study team. A separate local spreadsheet will be created by data extractors including only those identifiers needed to abstract the medical record. Identifier data elements will only be recorded on this spreadsheet as necessary to achieve the research purpose. This spreadsheet must be maintained securely, and access will be limited to the local co-investigator and study team. If any physical research records exist, they will be maintained in a secure location where access will also be limited to approved personnel at the local participating institution or site.

A description of this registry is available on www.ClinicalTrials.gov, for publication purposes.

6.3 Security

All REDCap data will be stored on Cedars-Sinai's servers and is 21 CFR part 11 compliant.

7.0 Data/Specimen Analysis and Statistical Plan (N/A FOR THIS REGISTRY)

7.1 Statistical Plan

7.2 Primary and Secondary Endpoints

7.3 Statistical Methods

7.4 Sample Size and Power

Appendix 1: List of Collaborating Sites

Additional sites to be added.

Columbia University New York, NY	**University of California, Davis** Davis, CA
Duke University Durham, NC	**University of California, San Francisco** San Francisco, CA
St. Luke Health System Kansas City, MO	**UT Health Science Center at Houston** Houston, TX
University of Arizona Tucson, AZ	**UT Southwestern Medical Center** Dallas, TX
Boston Medical Center Boston, MA	**Mount Sinai Medical Center** New York, NY
Johns Hopkins University Baltimore, MD	**Medical University of South Carolina** Charleston, SC
NYU New York, NY	**Scripps Health** San Diego, CA
Washington University St. Louis, MO	**Tufts Medical Center** Boston, MA
University of San Diego San Diego, CA	**University of Pennsylvania** Philadelphia, PA
Massachusetts General Hospital Boston, MA	**University of Utah** Salt Lake City, UT
MedStar Health and Vascular Institute/Georgetown University School of Medicine Washington, D.C.	**Cornell University** Ithaca, New York
Thomas Jefferson University Philadelphia, Pennsylvania	**University of Calgary** Calgary, Alberta
University of Washington Seattle, Washington	

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