REGISTRY PROJECT PLAN

1. Introduction

Mitral and tricuspid valve disease are prevalent cardiac conditions affecting millions of people worldwide, with significant implications for mortality and morbidity (1,2). The management of patients with mitral and tricuspid valve disease may include surgical or transcatheter interventions, depending on the indications, contraindications, risks, and benefits of each procedure (3,4). Importantly, the initial choice of treatment is of great consequence for the ensuing path of specific treatments a patient will undergo. Thus, multiple decisions are required at different stages in a patient's lifetime even though no ideal and clear-cut solution and timing currently exists. Suboptimal decision-making can lead to increased adverse outcomes and reduced quality of life for patients (5). A shift towards a lifetime-oriented approach to mitral and tricuspid valve disease which considers the (un)natural history of it at all ages is needed to optimize decision-making in mitral and tricuspid valve disease and thereby improve patient-outcomes. The Heart Valve Society (HVS) Mitral and Tricuspid Valve Database provides a suitable framework for compiling all components relevant to generating such an approach.

The HVS Mitral and Tricuspid Valve Database is a centralized registry in which individual centers (also called Partners) can share data according to a standardized data protocol. Collectively these partners form the HVS valve research network (VRN). Researchers can request access to the data to conduct studies according to a data access mechanism. The HVS Mitral and Tricuspid Valve Database operates under the auspices of the Heart Valve Society, a non-profit organization dedicated to improve outcomes patients with heart valve disease.

2. General objectives

The HVS Mitral and Tricuspid Valve Database is aimed to improve outcomes for patients undergoing interventions for mitral and/or tricuspid valve disease, to enhance uniform scientific reporting, to optimize multidisciplinary patient care, to assess quality of care and to update and improve guidelines. This is done through the specific research projects using data resulting from this registry.

3. Database design

Longitudinal observational cohort.

4. Study population

The HVS Mitral and Tricuspid Valve Database is a registry that collects data on the characteristics, procedural information, and outcomes of adult patients with mitral and/or tricuspid valve disease, who undergo surgical or transcatheter interventions.

5. Legal basis

Legal basis for the collection of patient data is based on local medical ethical review approval, with informed consent, unless there is an exception for consent on basis of applicable law if applicable. Within each individual center the data may be collected retrospectively and prospectively, according to the local medical ethical protocol. In order to enhance the amount of data collected individual centers are encouraged to follow an ambispective design. The start date specified in the local medical ethical protocol is considered the start data of prospective data collection. The data is made available to the HVS Mitral and Tricuspid Valve Database for further research under the specification outlined in the Joint Data Registry Agreement.

6. Database structure

Study parameters/endpoints

Partners collect data using the standardized data definition as specified in the HVS data dictionary (https://heartvalvesociety-vrn.org/documents), which is aligned with the Heart Valve Disease data set, developed by the International Consortium for Health Outcomes and Measurements (ICHOM) and includes baseline patient characteristics, procedural information, and outcomes (6).

Baseline data

Baseline data covers the following patient characteristics: demographics, diagnosis, and potential risk factors for operative mortality (EuroSCORE ||).

Procedural information

Procedural variables include detailed peri-procedural data, additional clamp session and complications at discharge.

Clinical / echocardiographic / patient reported outcomes

Outcome data includes clinical outcomes such as complications and possible reinterventions, longitudinal echocardiographic and additional MRI data, and patient-reported outcome measures. The patient-reported outcome measures include the EQ-5D-5L. The EQ-5D-5L questionnaire is currently available in over 170 languages.

Frequency of data collection

Data will be collected from medical records at baseline and during at least yearly follow by the individual partners. If patients are eligible for inclusion before the start date of prospective enrolment, baseline and (yearly) follow-up data will be extracted entirely retrospectively. Patients are followed until the end of follow-up due to (elective) retraction or death.

7. Modes of data transfer

Data may be transferred to the HVS Mitral and Tricuspid Valve Database either by a direct case-by-case method using a web-based Case Report Form in a secure data-entry system or by batch uploads which are send to the coordinator via secured file transfer systems. The data entry system is set up according to Good Clinical practice (GCP) guidelines and is compliant with the United States Food and Drug Administration (FDA) (21 CFR part 11), the General Data Protection Regulation (GDPR) and the Health Insurance Portability and Accountability Act (HIPAA).

8. Governance

The HVS Mitral and Tricuspid Valve Database is officially declared as a Valve Research Network (VRN) of the Heart Valve Society (HVS). The HVS Mitral and Tricuspid VRN consists of the participating centers (Partners), the Core Leaders, the Scientific Committee, the Data Management Team and the HVS board (Figure 1). All members of the HVS Mitral and Tricuspid VRN are welcome to join the Valve Research Network meetings. Controllership is governed by a Joint Data Registry Agreement, which participating centers sign upon joining the database. All participating centers are considered joint controllers and have designated a Core Leaders team to make executive decisions, a Scientific Committee to review research proposals (including data access requests), and a coordinator to process data on behalf of the controllers.

Participating centers (Partners)

Participating centers form the core of the Mitral and Tricuspid VRN. These centers collect data on patients undergoing mitral and tricuspid valve interventions and opt into the database as joint controllers, enabling multicenter research opportunities. The current partners of the database are specified at https://heartvalvesociety-vrn.org/participants-2/. Each center serves as controller with responsibilities to protect the personal data it contributes to the database. Each individual center is the owner of its own submitted data and is responsible for its accuracy and content. Data from individual centers are not accessible for any other center. Each participating center must have at least one member affiliated with the HVS. Local medical ethical regulation is the responsibility of the participating center.

Core Leaders

The Core Leaders are the executive organ of the HVS Mitral and Tricuspid VRN, and are mandated by the Partners to make executive decisions regarding the HVS Mitral and Tricuspid Valve Database. Their tasks in include governance and management regarding the HVS Mitral and Tricuspid Valve Database collection, adjustments of legal documents if appropriate, to review and approve the final Project Plan and Amendments, to monitor progress of data sharing, to select the network of investigators, to monitor progress of study enrolment of centers, to address and resolve study management problems and to secure sustainable finances. Core Leaders meet monthly to discuss ongoing matters and decisions are made on consensus basis. The position and name of current Core Leaders are described in Table 1.

Position	Name	Center
Chair	Evaldas Girdauskas, MD, PhD	University Hospital Augsburg (Germany)

Chair	Michele De Bonis, MD	Vita-Salute San Raffaele University (Milan)
Member	Marta Sitges, MD, PhD	Cardiovascular Institute at Hospital Clínic de Barcelona (Barcelona)
Member	Vinod Thourani, MD	Piedmont Heart Institute (USA)
Member	Victoria Delgado, MD, PhD	University Hospital Germans Trias i Pujol (Spain)
Member	Ralph Stephan von Bardeleben, MD, PhD	University Medical Center of Mainz (Germany)

Table 1: Core Leaders HVS Mitral and Tricuspid Valve Research Network

In case of rotation of Core Leaders, the participating centers (Partners) will be notified via e-mail, and added as amendment to this protocol.

Scientific Committee

The Scientific Committee consists of 7 members, including at least 2 cardiologists, 2 surgeons and 2 scientists. Members of the committee will serve for 3 years. After their term they have to wait 3 years before they can apply again. The Scientific Committee reviews research proposals and scientific papers originating from the registry. The Scientific Committee approves research request by filling out a standardized form following an e-mail-based procedure. The current composition of the Scientific Committee members is described in Table 2.

Position	**Name**	**Center**
Member	Marianna Adamo, MD	ASST Spedali Civili di Brescia (Italy)
Member	Jasimuddin Ahamed, PhD	Oklahoma Medical Research Foundation (USA)
Member	Rebacca Hahn, MD	Columbia University Irving Medical Center (USA)
Member	Hoda Hatoum, PhD	Michigan Technological University (USA)
Member	Meindert Palmen, MD, PhD	Leiden University Medical Centre (The Netherlands)
Member	Kevin Veen, MD, PhD	Erasmus University Medical Center (The Netherlands)
Member	Moritz Wyler von Ballmoos, MD, PhD	Texas Health Harris Methodist Hospital (USA)

Table 2: Scientific Committee HVS Mitral and Tricuspid Valve Research Network

In case of rotation of scientific committee members, the participating centers will be notified by e-mail, and added as amendment to this protocol.

Data Management Team (Coordinator)

All partners agreed to appoint one partner who is responsible for management and processing data in the registry. This is called the coordinator (synonym data management team). Currently the Coordinator is Erasmus MC, located in Rotterdam, The Netherlands. The Coordinator is the first point of contact regarding practical issues. Processing tasks include, but are not limited to, preparing datasets to be used by researchers, creating annual feedback and benchmark reports for centers, and monitor timely entry of data.

HVS board

The HVS Mitral and Tricuspid Valve Database operates under the auspices of the HVS, meaning the registry can leverage on the extensive network of the HVS and make use of HVS branding. The HVS is however not considered an joint-controller of the data and does not have access to the data. The HVS may promote the HVS Mitral and Tricuspid Valve Database and (at least one individual) of a Partners institution should be a paying member of the HVS.

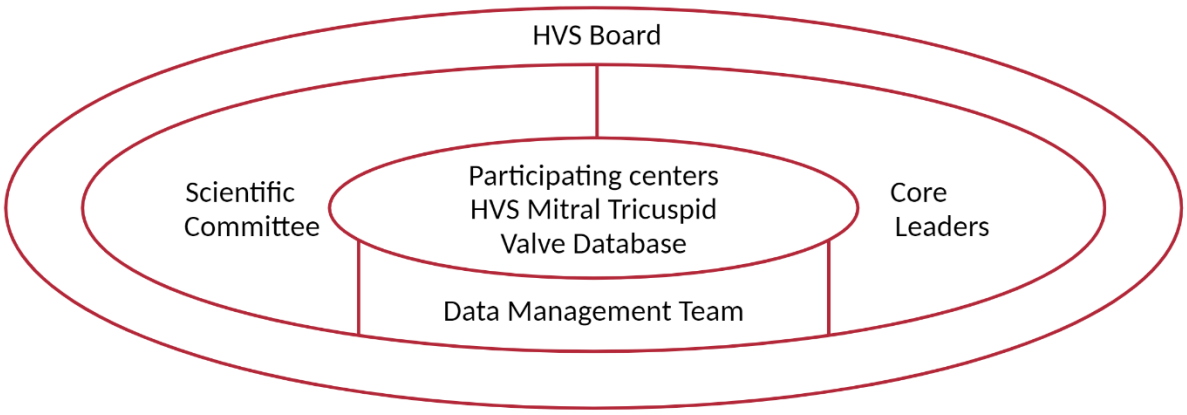

Figure 1: Governance HVS Mitral and Tricuspid Valve Research Network

9. Data Access mechanisms

Data can be accessed for the use of a study according to the following data access mechanisms.

Single Center data access by Partner

Each center can extract his own submitted data for local analysis. Online extractions can be performed whenever desired. Within the online application, reports and graphs will be developed. Individual center data are not visible for any other center. In a report with summary statistics single center data will be presented aside with aggregated results of the entire database. Data of centers other than your own are only visible for the Database Management Team (Coordinator) for the purpose of data validation to enhance data quality. Partners asked to mention the HVS Mitral and Tricuspid Valve Database when single center results based on data standards of the registry are presented or published, however this is not mandatory.

Multicenter data access by Partner

Research proposal

For analysis of multicenter data, a scientific research proposal is needed. Applications should be submitted to the Scientific Committee. Research proposals follow a standardized structure (https://heartvalvesociety-vrn.org/submit-a-research/). Before Partners submit a research proposal, they are advised to contact the data manager to assess feasibly of the research study and overlap with ongoing research. If this is not the case the database manager will receive the proposal and send the proposal to the Scientific Committee.

The data manager will send the research proposal to the Scientific Committee. The Scientific Committee will review the proposal to assess the validity of the research question and proper use of the data. The Scientific Committee can reject, accept or accept the proposal with changes. The researchers will receive 1 round of feedback on their proposal. The Scientific committee will review the researcher's response and accept or reject. In case of no consensus the proposal is discussed in the Core Leader meeting.
Each partner of whom data can be used in the research will be notified about the accepted proposal, and their data will be used if they do not oppose within two weeks (non-opposition procedure). If a partner opposes to the use of their data, they should justify their opposition to the Scientific Committee.
The research team will receive a double-pseudonymized data set, without patient and center identifying variables. After data extraction by the database manager, the researcher team will be given a deadline of 6 months to perform the analysis and write a draft publication (Figure 2). If the deadline is exceeded, the topic can be passed on to another research team.

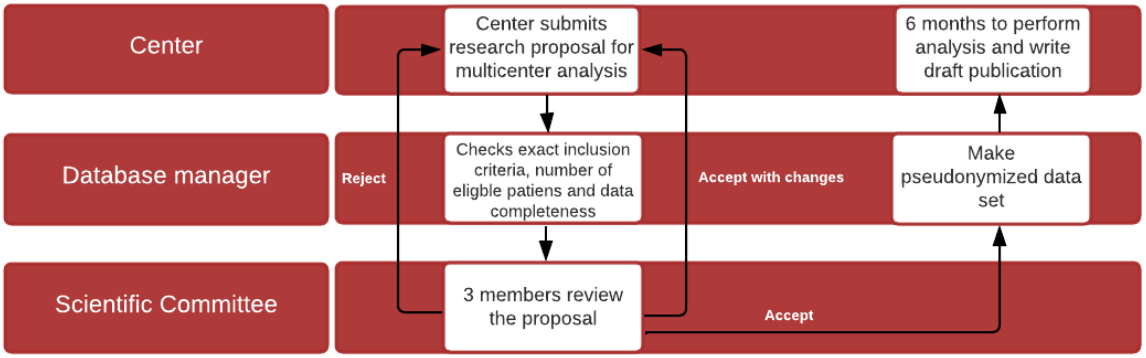

Figure 2: Request multicenter research by research proposal.

Project-proposal

Centers are able to request data by proposing a project. Projects are defined as a pre-specified patient population within mitral and/or tricuspid valve disease domain and pre-specified timeframe of collection, which can be retrospective or prospective data collection. Partners embarking on a project are responsible for their own local medical ethical board or IRB approval. The HVS Mitral and Tricuspid Valve Database is used as effective tool to share and reuse the data. Data collection in the project should adhere to the HVS Mitral and Tricuspid Valve Database data standards. Centers do not have to be a Partner when they propose a project but will have to become a Partner to participate.

Applications should also be submitted to the Scientific Committee. Research proposals follow a standardized structure (https://heartvalvesociety-vrn.org/submit-a-research/). Before Partners submit a research proposal, they are advised to contact the data manager to assess feasibly of the research study and overlap with ongoing research. If this is not the case the database manager will receive the proposal and send the proposal to the Scientific Committee.

The data manager will send the research proposal to the Scientific Committee. The Scientific Committee will review the proposal to assess the validity of the research question and proper use of the data. The Scientific Committee can reject, accept or accept the proposal with changes. The researchers will receive 1 round of feedback on their proposal. The Scientific committee will review the researcher's response and accept or reject. In case of no consensus the proposal is discussed in the Core Leader meeting. Subsequently the proposal will be discussed in the Core Leaders' meeting, and they will make a final decision.

Each partner of whom data can be used in the research will be notified about the accepted proposal, and their data will be used if they do not oppose within two weeks (non-opposition procedure). If a partner opposes to the use of their data, they should justify their opposition to the Scientific Committee.
The research team will receive a double-pseudonymized data set (if applicable within the project scope), without patient and center identifying variables. After data extraction by the database manager, the researcher team will be given a deadline of 6 months to perform the analysis and write a draft publication (Figure 2). If the deadline is exceeded, the topic can be passed on to another research team.
After the project is completed, all participating centers can request the multicenter data within this project.

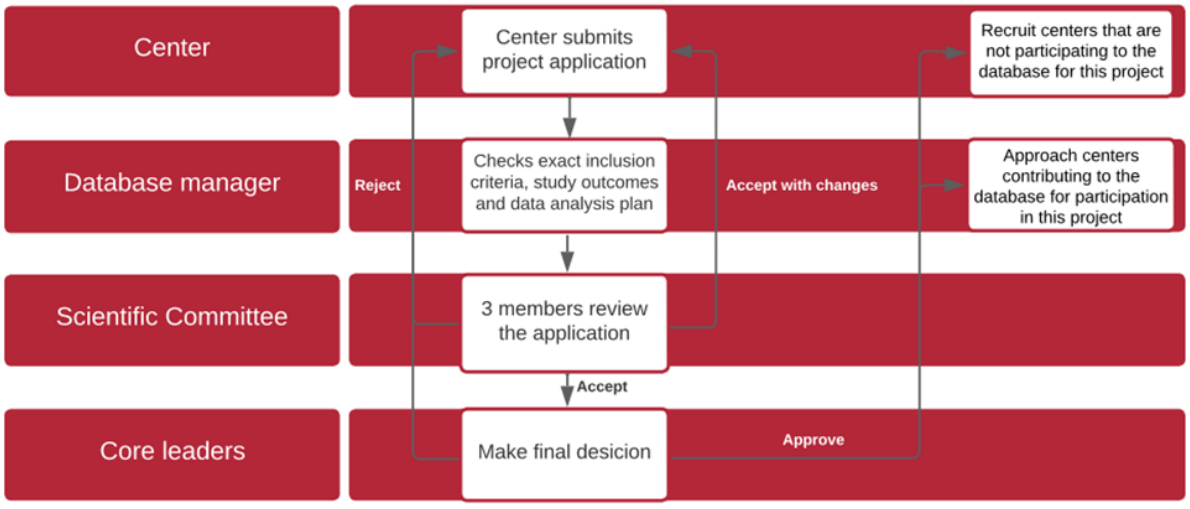

Figure 3: Project Proposal

Non-Partner access

The existence and maintenance of the database are dependent and made possible through the funding provided by external parties. In exchange for their crucial support, partners may share the data anonymously with these funding entities, in collaboration with a Partner. Thus, prior to any data exchange with these parties, aside from pseudonymizing the data after each extraction, anonymization procedures are implemented to guarantee patient privacy and adhere to legislations. To anonymize data to be shared with external parties, the key files generated after each extraction, as described above, will be destroyed by the coordinator. Additionally, all external collaborators will be bound by confidentiality agreements, reinforcing our commitment to ethical data handling. Any data provided by the HVS Mitral and Tricuspid Valve Database Registry to a Non-Partner is subject to separate Data Transfer Agreements, and subject to unanimous decision by the Core Leaders, even if a Partner is involved in the study.

10. Publication

Researchers who want to publish papers based on the HVS Mitral and Tricuspid Valve Database must send end products to the Scientific Committee for review. The Scientific Committee will check the quality and accuracy of the analysis and congruence with the Research Proposal and may suggest possible improvements with a maximum of two rounds. Researchers can revise their work accordingly. The Scientific Committee can halt publication of the manuscript if the quality is not deemed satisfactory after two rounds of feedback or is incongruent with the Research Proposal. In this case the Scientific Committee and researchers will meet and discuss a suitable solution.

Authorship

Authorship will be awarded according to the latest ICJME guidelines for authorship criteria (8) and amount of data supplied for the research. Data selection from the entire database will take into account data completeness. Follow-up completeness will be represented with the C* ratio: the total observed follow-up years divided by the total potential follow-up years (taking the observed death rate into account) (9). Each selected center can propose at least one author for the studies using its data. Authors will be listed based on their ranking in data completeness divided by 100 and multiplied by volume (from high to low). The number of authors will depend on journal requirements. Ideally, all participating partners in the research dataset will be represented or publish under an author group. In case there is a limit, centers with the highest ‘data quality *volume factor’ will come first

11. Data quality

The quality of the data stored in the HVS Mitral and Tricuspid Valve Database is crucial for ensuring reliable and accurate publications. To guarantee the quality of the data and analyses, the following measures are taken:

a. The data dictionary
b. Monitoring timely and complete entry
c. Feedback and benchmark reports

<u>The data dictionary</u>

The HVS Mitral and Tricuspid Valve data dictionary describes all variables for each registration. It

provides definitions for each variable, specifies whether it is required or not, and outlines the allowed values. Variables that are not allowed will be declined in the eCRF.

Monitoring timely and complete delivery

The Coordinator monitors the delivery and completeness of the submitted data. If a center fails to submit its data on time or if the data is incomplete, the center is requested to provide the missing information.

Feedback and benchmark reports

Feedback and benchmark reports are generated annually for each center. These reports assess the completeness and correctness of the data and compare them with other centers in the database. Based on these reports, centers are requested to supplement their data.

12. Patient Identifiable Data

When centers put the data in the eCRF, a patient code is automatically generated by the data capture system. This patient code is unique to each patient, and the identifying key file remains with each participating center. Individual center data are not visible for any other center.

Any information from this study, if published in scientific journals or presented at scientific meetings, will not reveal patient identities. Collected data will be secured against unauthorized access.

Researchers requesting data from multiple centers receive datasets where center codes are double-pseudonymized to ensure that clustering of patients within a center remains unobservable. This measure is necessary because subject IDs in the registry, by default, include center codes, which could potentially reveal large centers' identities. During this process, all subject IDs are replaced with randomly generated combinations of letters and numbers, unique to each data extract. The original subject ID keys are securely stored in separate key files managed by the Coordinator. If full anonymization is required, these key files are permanently deleted.

13. Costs and funding

For Partners joining the HVS Mitral and Tricuspid Valve Database is free of cost. Partners are not provided fees for sharing data. The HVS Mitral and Tricuspid Valve Database operates under a cost-recovery model to cover the cost made by the coordinator in managing the registry.

14. References

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