Protocol HVS Mitral Tricuspid Valve Database

1. Introduction

Mitral and tricuspid valve disease is a common condition that affects millions of people worldwide and has a significant impact on mortality and morbidity (Aluru et al., 2021; Roth et al., 2020).

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 (Besler et al., 2021; Karam et al., 2020). Surgical interventions include valve repair or replacement with mechanical or bio prosthetic valves, while transcatheter interventions include edge-to-edge repair with clips or annuloplasty with rings or bands (Karam et al., 2020; Kowalewski et al., 2019).

However, the treatment of patients with mitral and tricuspid valve disease is not straightforward and poses challenges and uncertainties. Despite the major progress in the last decades and the rapid innovations in the surgical and catheter-based field, there are still many unresolved issues and knowledge gaps in this area. For example, not every patient with secondary mitral regurgitation responds positively to mitral valve intervention and those who benefit remain to be better defined Kowalewski et al., 2019; Nishimura et al., 2017). However, there has been a conceptual change in the surgical mitral valve repair with an increasing focus on left-ventricular geometry to counteract left-ventricular remodeling (Kowalewski et al., 2019; Nishimura et al., 2017). Patients with secondary mitral regurgitation and severe leaflet tenting may benefit from simultaneous subannular repair that can be added to a standard mitral valve annuloplasty (Kowalewski et al., 2019).

Also, the treatment methods of patients with tricuspid valve present inherent complexities. The tricuspid valve has a unique anatomy and physiology that poses specific difficulties for transcatheter interventions, such as the risk of entrapment, conduction disturbances, coronary compression, and device positioning (Chang et al., 2021). Moreover, the indications for tricuspid valve surgery are not well established and depend on many factors, such as the cause, severity, and effects of tricuspid regurgitation, and the presence of left-sided heart valve disease (Rodés-Cabau et al., 2016). Therefore, there is a need for more evidence and guidance on the optimal management of patients with tricuspid valve disease.

From here starts the international HVS Mitral Tricuspid Valve Database initiative, one single platform to allow a fair comparison between all techniques and devices dedicated to mitral and tricuspid valve treatment. To achieve this goal, long-term robust data on mitral and tricuspid valve repair and replacement are needed. However, most studies are observational and report on single devices or techniques with inadequate reporting of valve-related events. Moreover, current registries do not allow detailed analysis by etiology and usually have limited follow-up. Finally,

as shown by the first-ever global examination of the medical device industry (ICIJ, 2018), health authorities have failed to protect patients from poorly tested implants, highlighting the need for more traceability. Therefore, novel surgical techniques for mitral and tricuspid valve repair must be compared with other treatment options in a real-world scenario, including catheter-based procedures and valve replacement.

To facilitate a coherent discourse for cardiologists and cardiothoracic surgeons treating and informing patients with heart valve disease, the International Consortium for Health Outcomes Measurement (ICHOM) has provided a framework for outcome measures (ICHOM, 2023). This framework will be used in the database as a baseline of outcome measures. ICHOM is an international non-profit organization that aims to achieve value-based healthcare by defining global standard sets of outcome measures that really matter to people (ICHOM, 2023). Their work is crucial in helping surgeons and patients choose the best treatment option by comparing long-term outcomes of patients after different therapies.

2. 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.

3. Study design

The study design is a longitudinal observational cohort study conducted across multiple centers. The database structure is configured as a prospective observational cohort study with an ambispective component, facilitating both retrospective and prospective patient inclusion with subsequent follow-up. This hybrid design was selected to facilitate the observation of various short- and long-term outcomes, necessitating early long-term follow-up from the inception of the database. Patient inclusion before center participation is classified as part of the retrospective aspect within the ambispective design. It involves the utilization of medical records to assess the quality of healthcare retrospectively and conduct healthcare evaluation research prospectively.

4. Study population

The HVS Mitral and Tricuspid Valve Database is a registry that collects data on the characteristics, procedural information, and outcomes of patients with mitral and/or tricuspid valve disease who undergo surgical or transcatheter interventions. Incapacitated adults are excluded. The registry is open to centers that perform these interventions. Patients can be included consecutively, or project based.

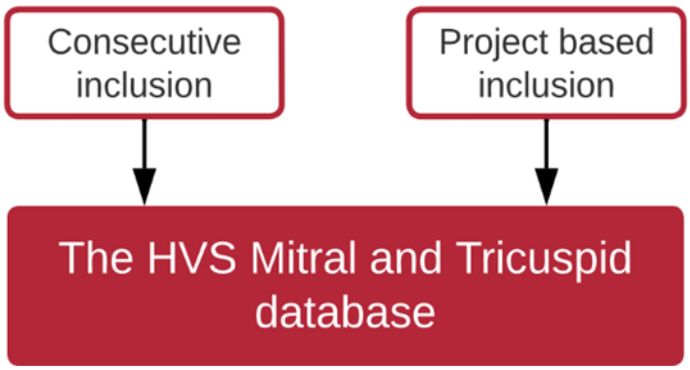

Figure 1: Inclusion flowchart

5. Application process

Centers can enroll patients with mitral and/or tricuspid valve disease consecutively or apply project based. However, it is highly recommended that centers contribute as much data as possible to achieve the study objectives, facilitate the extraction of their own outcomes, and increase their access in the application for multi-center analysis.

Centers that participate consecutively enroll all patients who have undergone an intervention for mitral and/or tricuspid valve disease. They need to fill in the Clinical Study Site Agreement (CSSA). Centers add patients to the database both retrospectively and prospectively.

Centers that participate as part of a project enroll a specific group of patients who have undergone an intervention for mitral and/or tricuspid valve disease, within a defined time. They can propose a project or join an existing one. By joining an existing project, the application is the same as for consecutive patients' inclusion, only the scope of included patients is limited.

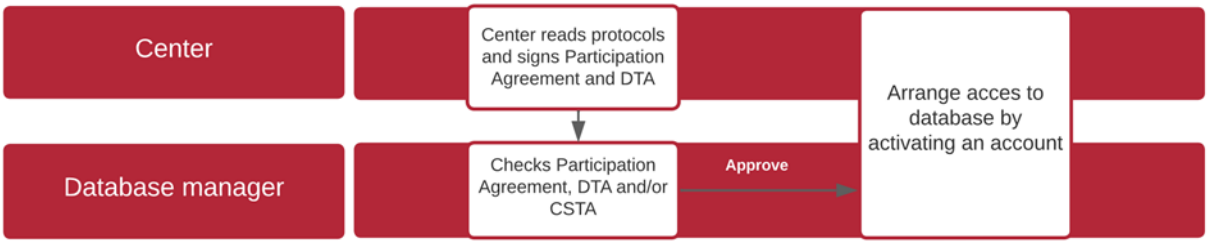

Figure 2: Application process

6. Methods

Research methods

The study database will be accessible for patient enrollment starting in March 2024. Data will be extracted from medical records at baseline and during yearly follow-ups by qualified research staff. If patients are eligible for inclusion before the prospective enrollment start date, baseline and yearly follow-up data will be extracted retrospectively from 1985. The extracted data will be entered into an electronic Case Report Form (eCRF) in Castor EDC, which can be completed either manually or through batch uploads.

Additionally, the Study Site will collect data using patient-reported outcome measures (PROMs). The questionnaire will be administered before the procedure, at discharge, and annually thereafter. This process will take place within the hospital premises at admission and discharge by qualified research staff, after obtaining informed consent (see 12. Ethical considerations). Subsequently, the questionnaire will be sent annually via email or post.

Study parameters/endpoints

The collected data is based on the Heart Valve Disease data dictionary from the International Consortium for Health Outcomes and Measurements (ICHOM) and includes baseline patient characteristics, procedural information, and outcomes (ICHOM, 2023).

<u>Baseline data</u>
Baseline data covers the following patient characteristics: demographics, diagnosis, and potential risk factors for operative mortality (EuroSCORE), as also specified by the ICHOM initiative.

Procedural information

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

Clinical / echocardiograpic / 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. Outcomes are defined according to the international ICHOM standards (ICHOM, 2023). The patient-reported outcome measures include the EQ-5D-5L. The EQ-5D-5L questionnaire is currently available in over 170 languages.

7. Analysis and proposals

Data controllership and online analysis

The HVS Mitral and Tricuspid Valve database system is owned by the Heart Valve Society (HVS), which is responsible for the technical maintenance. Centers and HVS sign a joint-controllership agreement about the collected data. Online extractions can be performed whenever desired, and within the online application, reports and graphs will be developed. Individual center data are not visible to any other center. In a report with summary statistics, single-center data will be presented alongside aggregated results of the entire database.

Single center analysis

Each center can extract its own submitted data for local analysis. The center must inform the HVS of any publication involving single-center data and acknowledge the HVS Mitral and Tricuspid database as the collecting platform. The HVS Mitral and Tricuspid database will not limit, nor check these publications. For analysis of multicenter data, a scientific research proposal is required. Applications should be submitted to the Scientific Committee.

Multi center analysis

Research proposal

Active participants are allowed to perform research using multicenter data. To submit a research proposal, participants must contact the data manager. The exact patient population and included forms that should be selected for the research project will be defined by the data manager and researcher. The research proposal should not overlap with an ongoing project, either a project or another research proposal.

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 researchers response and accept or reject. In case of no consensus the proposal is discussed in the core leader meeting. Each center which can participate in the study will be notified about the accepted proposals and their data will be used automatically (non-opposition procedure). If a center does not agree, his opposition should be justified to the SC within 2 (two) weeks. The research team will receive a pseudonymized data set, without patient and center identifying variables. After data extraction, the team will be given a deadline of 6 months to perform the analysis and write a draft publication. When the deadline is exceeded, the topic can be passed on to another group.

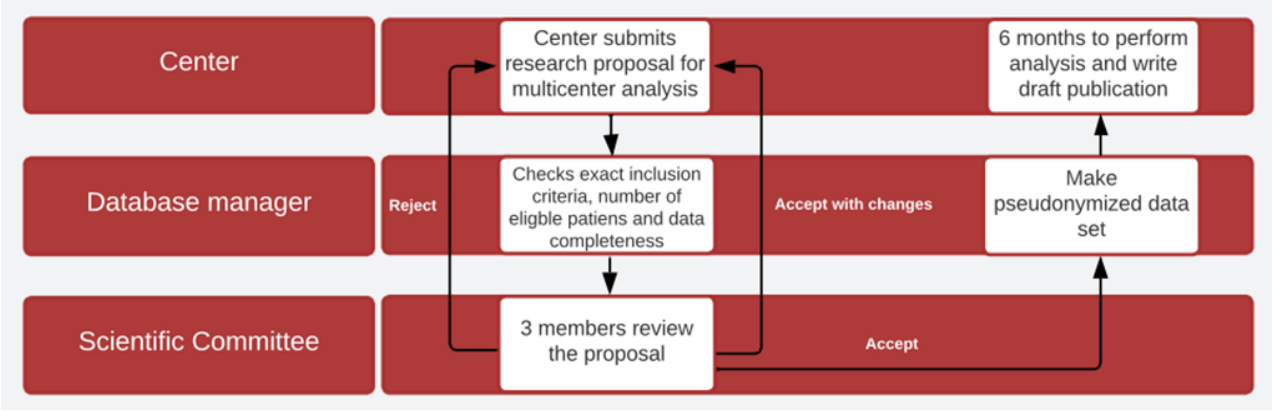

Figure 3: Request multi center research by research proposal.

Project-proposal

If centers wish to propose a project, they should complete and submit the Project Application Form to the Scientific Committee for approval. First, the data manager checks the exact inclusion criteria, study outcomes and data analysis plan. The Scientific Committee will give one round of feedback on the proposal and the researchers. The researchers will adjust their proposal. Subsequently the proposal will be discussed in the core leaders' meeting. If not already participating in the database; the initiating researchers will be given an account for the database as specified in section 5.

If the proposal is approved, the database manager (together with the initiating researchers) will approach a) centers currently participating consecutive patients to the data if they are willing to participate to this project, b) approach centers currently not participating to the database if they are willing to participate in this particular project.

When a center initiates a project, multicenter research is initially only possible for the initiator of the project. The extraction of data is limited to the exact patient population and time as specified in the project proposal. Note that the data of centers that participate consecutively is also included, if they wish to participate.

As the project is already accepted by the Scientific Committee, the initiating research team can request a pseudonymized data set, without patient and center identifying variables. After data extraction, the team will be given a deadline of 6 months to perform the analysis and write a draft publication that should be presented at the next meeting. When the deadline is exceeded, the topic can be passed on to another group.

After the project is completed, all participating centers can request the multi center data within this project.

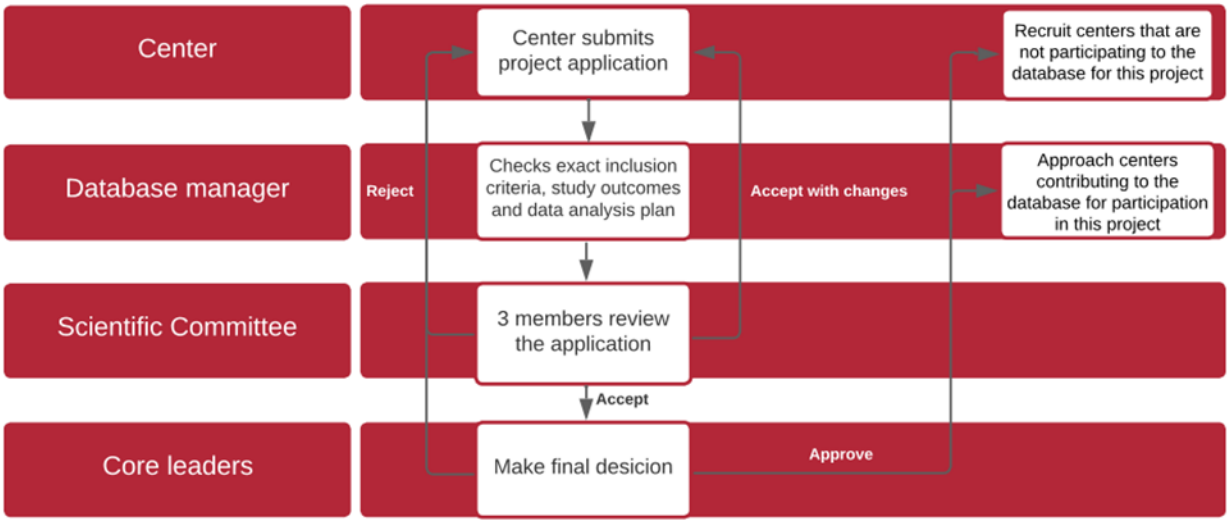

Figure 4: Project Proposal

8. Publication

Researchers who want to publish papers based on the 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 data and analysis and 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. 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. The authorship order for a research based on a research proposal or project is as follows: the first and second authorship are for the person who performed the research, ideally young investigators. The last authorship is for the Principal Investigator (PI) of the proposal. Intermediate authors are those who meet the eligibility criteria based on the ICJME guidelines (e.g., active participation in writing and approval of the manuscript is necessary) and have contributed to data analysis and/or inclusion of data related to the specific research question. The order of these authors is determined by the completeness of the data.

Data selection from the entire database will take into account data completeness. It will be measured in sub modalities, like hospitalization data, clinical follow-up and echo follow-up. 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) (Wu et al., 2008).

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). Within research conducted in a set project, both centers that enroll consecutively and project-based are eligible for authorship. Project-based enrollment has priority over consecutive enrollment. The Scientific Committee shall determine the degree of priority fairly and rationally.

The number of authors will depend on journal requirements. Ideally, all participating centers in the research dataset will be represented. In case there is a limit, centers with the highest ‘data quality * volume factor’ will come first. If a center does not respond to a co-author request within 3 months, the authorship can be cancelled.

9. Data quality

The quality of the data stored in the HVS Mitral 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
d. Audits

The data dictionary

The Mitral 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 HVS data management team 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.

Audits

Biannual audits are conducted by the data management team to thoroughly examine the accuracy and completeness of the data supplied to HVS. The results of these audits are discussed in Valve Research Network meetings. Any striking or discrepant results are analyzed, and findings from these audits are used to continuously improve data quality. The audits are performed by the HVS data management team.

10. Data safety

The database in Castor EDC is set up according to Good Clinical practice (GCP) guidelines, is United States Food and Drug Administration (FDA) compliant (21 CFR part 11) and meets the criteria of European legislation (General Data Protection Regulation).

Patient Identifiable Data

Each patient will be assigned a study number, generated by Castor EDC, known by the principal investigator and delegated investigators of individual center and the HVS database management team. The individual center will create a file at their local department linking the coded study numbers to their respective patients. This linking file will remain at the individual center and will not be shared with the HVS data management team or others within the Valve Research Network. Any information from this study, if published in scientific journals or presented at scientific meetings, will not reveal patient identities.

Study period

The study period will last until 2050 (approximately 25 years after approval of this protocol). Data will be stored for a maximum of 15 years after the study period until 2065. After 15 years of storage, data will be destroyed.

11. Organizational structure

The HVS Mitral and Tricuspid Valve database is officially declared as a Valve Research Network (VRN) of the HVS. The HVS Mitral Tricuspid VRN consists of the core leaders, Scientific Committee, the data management team and the HVS board. The latter includes all participants of the registry, who are welcome to join the network meetings. The HVS Mitral and Tricuspid Valve Research Network follows the HVS policies and regulations. This allows any HVS member to join the HVS Mitral and Tricuspid Valve database freely. At least one member of each center should be a member of the HVS.

HVS Mitral and Tricuspid Valve Research Network

The members form the core of the Mitral Tricuspid VRN, which aim to bring together cardiologists, surgeons, and scientists interested in the field of mitral and tricuspid valve interventions. There is a biannual project meeting during the annual meeting of the HVS and EACTS (European Association for Cardio Thoracic Surgery), to which all participants are invited. A project update is given at these meetings, and the outcomes of research and/or audits originating from the registry are discussed.

Scientific Committee

The Scientific Committee consists of 7 members, including at least 2 cardiologists, 2 surgeons and 1 scientist. Members of the committee will serve for 3 years. After their term, they must wait 3 years before applying again. The Scientific Committee reviews project applications, research proposals and proposed abstracts and manuscripts originating from the registry.

Data Management Team

The data management team includes one general leader, the database coordinator, and the database manager. They are responsible for developing the database. Their tasks include setting up the database, recruiting centers, guiding the application process, collecting data, monitoring the quality of included data and initiating data quality enhancement. The data manager is the first contact for questions from participating centers related to the online database.

HVS board

The HVS board can be consulted for advice.

12. Ethical considerations

Regulation statement

The study will be conducted in accordance with the principles of the World Medical Association (WMA) Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (19 October 2013) and the WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks (October 2016). For more information, please visit the WMA website at www.wma.net.

Informed consent

Every center participating in the Mitral Tricuspid Valve database is responsible for ensuring that informed consent is obtained from patients, in accordance with national requirements regarding informed consent. Only patients who have provided informed consent can be included in the database. However, in other cases, for example where patients are included retrospectively, the center is responsible for ensuring that a lawfully accepted exception is applied, as no informed consent will be signed.

13. References

1. Aluru JS, Barsouk A, Saginala K, et al. Valvular Heart Disease Epidemiology. Medical Sciences. 2021;10(2):32.
2. Roth GA, Johnson CO, Nguyen G, et al. Global, Regional, and National Burden of Calcific Aortic Valve and Degenerative Mitral Valve Diseases, 1990–2017. Circulation: Cardiovascular Quality and Outcomes. 2020;13(1):e006093.
3. Besler C, Blazek S, Rommel KP, et al. A Practical Approach to Combined Transcatheter Mitral and Tricuspid Valve Repair: A Single-Center Experience. Frontiers in Cardiovascular Medicine. 2021;8:706123.
4. Karam N, Praz F, Himbert D, et al. Mitral and Tricuspid Transcatheter Interventions Current Status and Future Directions. Frontiers in Cardiovascular Medicine. 2020;7:61.
5. Kowalewski M, Suwalski P, Pawliszak W, et al. Surgical treatment of functional mitral regurgitation: current concepts and future perspectives. Journal of Thoracic Disease. 2019;11(Suppl 10):S1533-S1545.
6. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(25):e1159-e1195.
7. Chang CC, Veen KM, Hahn RT, et al. Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy: a state-of-the-art expert review. European Heart Journal. 2021;42(28):2766-2782.
8. Rodés-Cabau J, Taramasso M, O'Gara PT, et al. Diagnosis and treatment of tricuspid valve disease: current and future perspectives. The Lancet. 2016;388(10058):2431-2442.
9. ICIJ. Medical Devices Harm Patients Worldwide As Governments Fail On Safety. ICIJ; 2018. Available from: https://www.icij.org/investigations/implant-files/medical-devices-harm-patients-worldwide-as-governments-fail-on-safety/ [Accessed 9 August 2023].
10. ICHOM. Value Based Healthcare, Improving Patient Outcomes. ICHOM; 2023. Available from: https://www.ichom.org/ [Accessed 14 August 2023].
11. ICHOM Connect. Heart Valve Disease – ICHOM Connect. https://connect.ichom.org/patient-centered-outcome-measures/heart-valve-disease/ [Accessed 14 August 2023].
12. Wu Y, Takkenberg JJ, Grunkemeier GL. Measuring follow-up completeness. Ann Thorac Surg. 2008;85(4):1155-7.