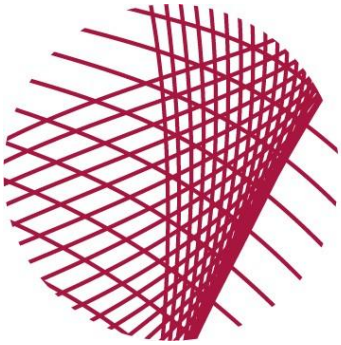

Universitäres
Herz- und Gefäßzentrum
UKE Hamburg

ARTORIA - R (p**A**tients p**R**esenting wi**T**h c**O**ngenital hea**R**t d**I**se**A**se -**R**egistry)

A register regarding the outcome of adult patients with congenital heart disease (ACHD) or inherited cardiomyopathies evaluated or listed for heart or heart and combined organ transplantation

Version 1.2 (16th October 2025)

Content

1. Synopsis

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Title of the study	PAtients pResenting wiTh cOngenital heaRt dIseAse -Registry
Acronym	**ARTORIA-R**
Condition	

Primary Outcome	The studied condition is the outcome of adult patients with congenital heart disease/inherited cardiomyopathy listed or evaluated for heart or heart and combined organ transplantation
Secondary Outcome	- Mortality while listed or following evaluation for transplantation - Delisting due to clinical worsening - Delisting due to clinical improvement
	- All-cause mortality following transplantation

Competing Outcome	- Transplantation - Durable ventricular assist device
Inclusion criteria	- All patients listed or evaluated for heart or heart and combined organ transplantation - Patient is classified as adult according to age in the country participating
Exclusion criteria	- Re-listing for organ transplantation after already being transplanted in the past with heart or heart/lung transplantation
Studycenter	Retrospective registry with prospective inclusion of patients presenting to the participating centers
	University Heart and Vascular Center Hamburg Department of Cardiology & Department of Cardiovascular Surgery Martinistr. 52 20246, Hamburg Germany Study coordinator: Dr. Christoph Sinning (c.sinning@uke.de)
Summary	Advances in surgical and medical care have led to improved outcomes in patients with congenital heart disease (CHD). As a consequence, the majority of patients nowadays survives to adulthood (adults with CHD, that is, adult CHD [ACHD]) with good quality of life. Despite the surgical success, the morbidity and mortality of ACHD is higher than in the general population and is linked to the development of heart failure (HF) in adulthood. HF occurs in approximately 25% of patients with ACHD, even in those patients in whom the congenital malformation has been corrected successfully in childhood. The time course and presentation are heterogeneous owing to variable congenital malformation and limitation of treatment options. ACHD with an anatomic right ventricle as the systemic ventricle (e.g., atrial switch operation in patients with transposition of the great arteries [TGAs]) and those with a functional single ventricle (e.g., Fontan circulation) appear to be at higher risk of developing HF. Young age at initial corrective surgery—often in the first 2 years of life—and lack of specific medical therapies can contribute to a high and early demand for heart transplantation in patients with ACHD. The primary aim of this study was to provide comprehensive data on patients with ACHD listed or evaluated for heart transplantation using data from the Eurotransplant registry, Organización Nacional de Trasplantes, Agence de la Biomédecine, Centro Nazionali Trapianti, NHS Blood and Transplant. Further, additional institutions and organisations have been contacted worldwide to add data to the register. Thus a representative data set of patients with ACHD listed for transplantation can be created and analysed for (1) underlying heart condition and repair, (2) clinical characteristics, and (3) factors associated with adverse outcomes in patients with ACHD listed for heart transplantation.
Keywords	Adults with congenital heart disease (ACHD), heart transplantation, ventricular assist device

2. Introduction

Background:

Heart failure represents a common end-stage syndrome for many adults with congenital heart disease (ACHD). These patients, however, have been excluded from most heart transplantation research. It is not known how current criteria, derived from non-ACHD populations, used to determine priority at the time of transplant listing, impact the outcomes for ACHD patients listed for heart transplantation. In the background of rising numbers of ACHD patients with currently 1 million in Europe and as well associated rare cardiomyopathies often as well related to ACHD, there is need to establish a database allowing for a better understanding of advanced heart failure in these patients [1-7].

3. Structure of the study

i. Aims of the study

Primary aims of the study:

The primary aim of the study is to collect data on adult patients with congenital heart disease or inherited cardiomyopathy (arrhythmogenic right ventricular cardiomyopathy, non-compaction cardiomyopathy or hypertrophic cardiomyopathy) evaluated or listed for heart and combined organ transplantation to establish a register which includes comprehensive data regarding the (**a**) type of congenital heart defect/inherited cardiomyopathy and previous treatment or repair in case of congenital heart disease (**b**) clinical characteristics and (**c**) allows to analyse factors associated with an adverse outcome in this cohort of patients or with the competing event of successful transplantation or treatment with a durable ventricular assist device. **Figure 1**.

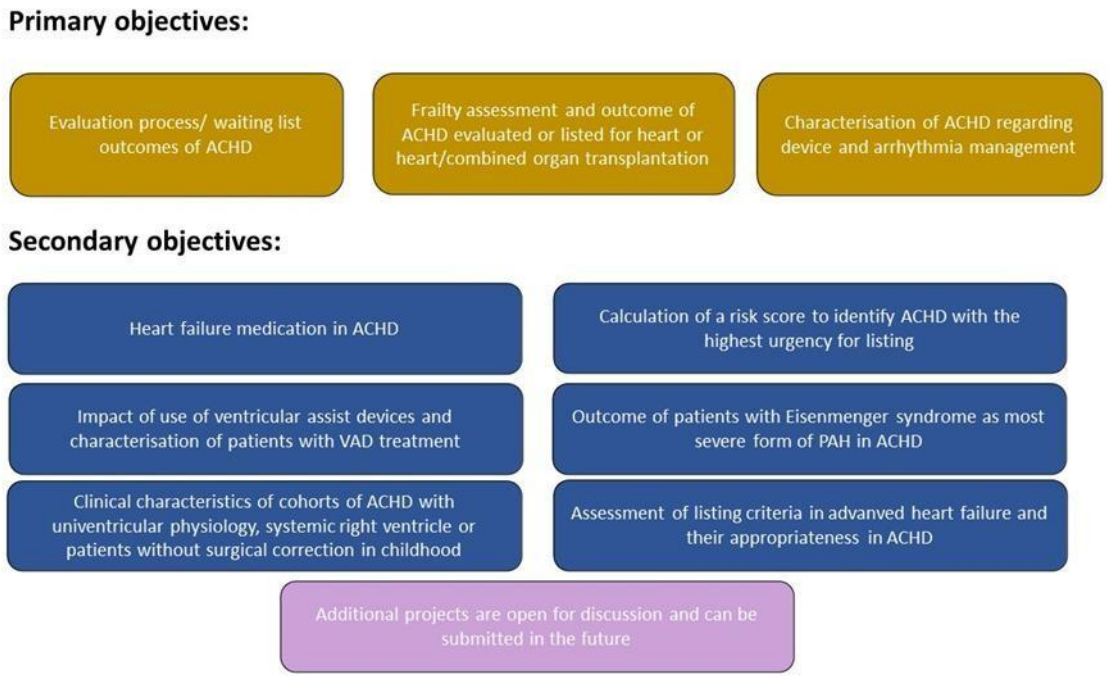

Figure 1 Primary and secondary study objectives

<u>Two major research outcomes should be addressed with this database:</u>

A. **"Waiting list outcomes of ACHD patients on the waiting list" and**

B. **"Impact of ICD/CRT therapy in ACHD patients while on the waiting list"**

<u>A.</u> <u>Waiting list outcomes</u>:

- Waiting list mortality and delisting due to clinical worsening is expected to be more common in ACHD patients due to the fact that these individuals often present in an advanced stage of terminal heart failure[7]. We will define different predictors for mortality and/or delisting in this patient cohort and as well describe the outcome in a meaningful database of patients
- Due to the decreasing number of organs available mechanical assist devices are an option for bridge to transplant or destination in mostly left ventricular heart failure. However, as ACHD patients often have a changed anatomy or both left and right ventricular failure, we want to describe the current method of treatment in ACHD patients.
- Description of heart failure treatment in patients with ACHD or inherited cardiomyopathies is often difficult since only few randomized studies are available or in case of ACHD treatment is related to expert consensus with evidence level C (in relation to the classification of evidence as pointed out by the European Society of Cardiology)

B. Impact of ICD/CRT therapy in ACHD patients:

- Description of distribution regarding ICD or CRT in patients with congenital heart disease with especially focus on anatomy of the systemic ventricle, presence and factors related to CRT therapy in these patients and important comorbidities which might limit life expectancy like pulmonary arterial hypertension
- In addition to device therapy treatment with specific antiarrhythmic therapy like use of amiodarone, sotalol, propafenone, flecainide or dofitilide to treat rhythm disorders like ventricular tachycardia or presence of additional rhythm disorders
- Pretreatment of the patients regarding rhythm disorders with previous ablation of atrial or ventricular tachycardias
-

Secondary aims of the study

The data collected in this register allow for a number of additional projects which are planned to be addressed more in detail. Especially patients with inherited cardiomyopathies are not often in the focus of heart failure research:

- In depth analyses of factors related to outcome in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), non-compaction cardiomyopathy and hypertrophic cardiomyopathy are each a secondary aim in conjunction with analyses as outlined for adults patients with congenital heart disease

ii. Design of the study

The ARTORIA-R study is a multicenter study including retrospective data from hospitals contributing to the national organ transplantation agencies [8]. The national transplantation societies were asked to contribute data to the register and invite hospitals to inquire the archives of each institution as the data requested is commonly not stored in electronic form. The data of all national hospitals are send to the national organ transplantation agency which transfers the pseudonymized data of each country to the Department of Cardiology of the University Hospital Hamburg which will analyze the data regarding the outlined primary and secondary endpoints. At the current time the data inquired is of the Eurotransplant region, Spain, Italy, France and the United Kingdom. However, in the future additional organ transplantation agencies might be contacted as well to contribute. Especially the institutions in

the United States of America, Canada for North America and the Asian countries Japan, South Korea and China in the Asian region have a high standard of treatment and a large number of patients treated and as well support a national organ transplantation program.

Important for the data transfer and analysis of the data are the two facts that the data of the patients is pseudonymized and cannot be followed back to the individual patient and that each of the national organ transplantation agencies did approve the project. **Figure 2**.

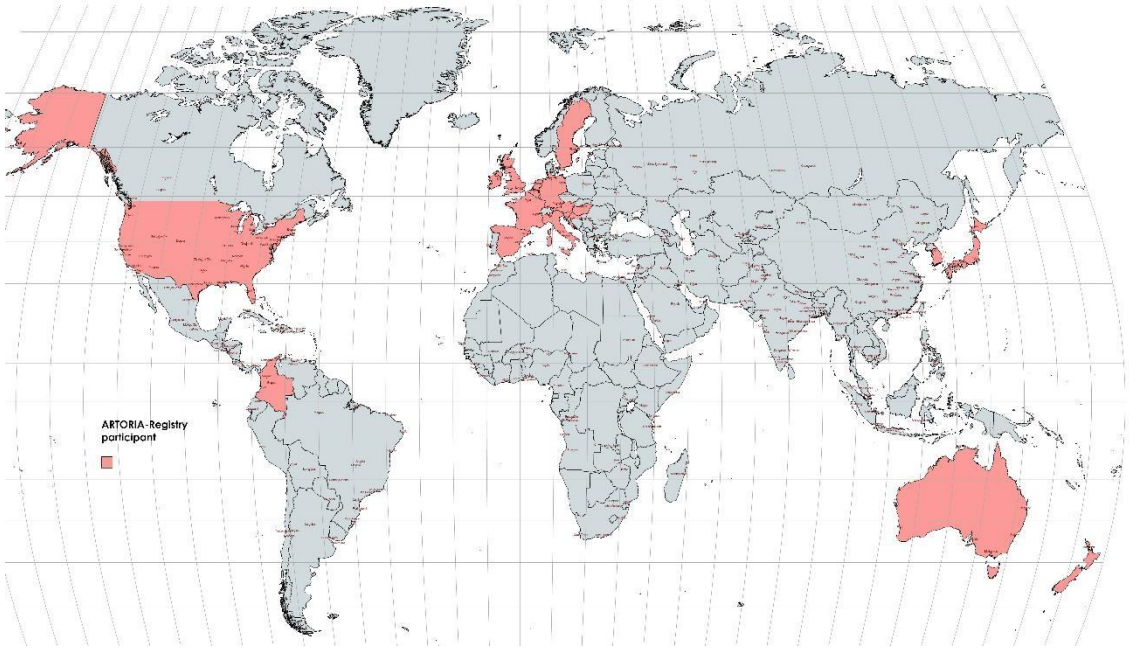

Figure 2 Current member countries of the ARTORIA-R

The study is registered at ClinicalTrial.gov (https://www.clinicaltrials.gov/) of the United States Library of Medicine with the identifier: NCT04848844 **iii. Concept of the study**

Data of all adult patients with congenital heart disease/inherited cardiomyopathy listed for heart or heart and additional organ transplantations can be included into the register. Data are collected by the hospital and transmitted to the national organ transplantation agency which retains a copy of the national data and submits the data for analysis to the Department of Cardiology of the University Heart Center Hamburg.

Current national organ transplantation agencies cooperating regarding the study

Eurotransplant; **Countries: Austria, Belgium, The Netherlands, Germany, Croatia, Luxemburg, Slovenia, Hungary**

Spanish National Transplant Organization (ONT); **Country: Spain**

NHS Blood and Transplant; **Country: United Kingdom**

Centro Nazionale Trapianti; **Country: Italy**

Agence de la Biomédecine; **Country : France**

iv. Study flow and follow-up

All data entered into the registry are of the first initial listing or evaluation of the patient to the waiting list/advanced heart failure therapy and are pseudonymized with a study ID. Important dates as date of birth or date of transplantation are only shown with month and year without the day. The data are transferred as pseudonymized (de-identified data to the University Heart Center Hamburg, Department of Statistics for analysis).

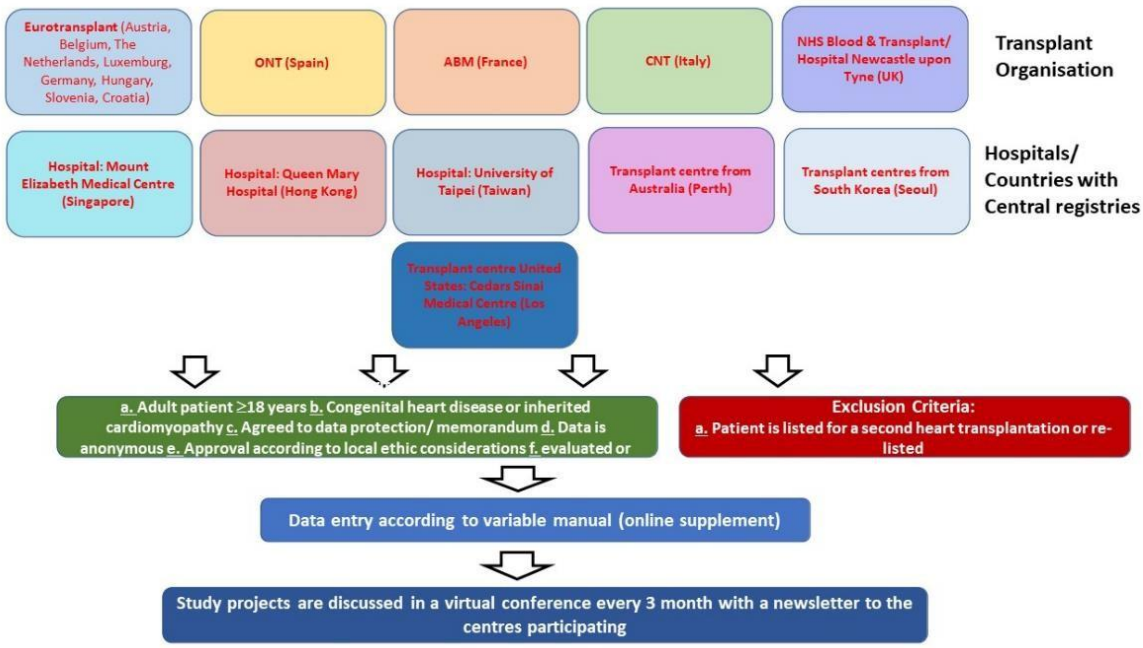

Figure 3 Study flow and inclusion of data into the study data base

Pilot study and harmlessness

The first results of the register resulting in the idea of a project combining the data of an increased number of organ transplantation agencies and as well countries are published[7]. Although the approach resulted in additional information regarding adult heart failure patients with congenital heart disease, it as well showed the limitations as the results are only true for a limited number of patients and a some parts of Europe. Thus also the pilot study did show the feasibility, data from additional regions and transplantation agencies are needed to contribute to new diagnostic and treatment aspects of ACHD patients with terminal heart failure.

Since only pseudonymized data are used there are no concerns regarding patients data safety as well that the study is of no concern regarding the physical health of the patient.

4. Study population

i. Patient cohort of the study

Study cohort:

ACHD/inherited cardiomyopathies (ARVC, arrhythmogenic right ventricular cardiomyopathy; NCC, non-compaction cardiomyopathy or HCM, hypertrophic cardiomyopathy) of patients listed or evaluated for orthotopic heart transplantation or combined heart and other organ transplantation (heart+lung, heart+kidney, heart+liver or 3 or more organs) during the time period 1989 to current date from the listed organ allocation institutions.

Patients listed for repeat transplantation are excluded.

ii. Inclusion criteria

- Patients have to be listed for heart or combined heart (meaning heart transplantation including at least one other organ) transplantation.
- The patient has to be classified as adult according to age criteria

iii. Exclusion criteria

- Patients for repeat transplantation are excluded

5. Data management and data safety

A. For retrospective included patient data

All centers contribute pseudonymized data to the study and as a reason of that the institution performing the statistical analyses (Department of Cardiology, University Heart Center Hamburg) cannot identify the individual patient. As such the study uses only de-identified data. In a second step the submitted data receives a new study ID and important dates, like date of birth or date of treatment are only shown with month and year without the actual date.

The interrogated study variables are attached to this document as a separate file (**supplement A – study variables**). The variables are selected to represent important results of the listing procedure of the patient, patient history, medical treatment and advanced heart failure treatment with devices like cardiac resynchronization or even with a ventricular assist device.

The hospitals are asked to collect the data of all ACHD patients or inherited cardiomyopathy as outlined during the time frame 1989 to current date retrospectively. All patients entered will receive a

pseudonym for each study center. The format of the pseudonym is a number-based code with the format:
XXX (country) – XXX (center) – XXXX (number of the patient starting with 1). Only the center and the sponsor of the study will know which code is corresponding to a specific center. Other centers of the same country will not have a list which code belongs to a certain center. All important dates in the study table (like date of birth or date of transplantation will be shown without the corresponding day in the format mm.yyyy (month.year). Thus, with this additional step of data minimization the investigators can prevent the identification of a certain, individual patient.

The data is collected with Excel sheets (**supplement B – Excel sheet of the study variables**) showing the study pseudonym ID for each center for the patient. The Excel sheets are imported into the REDCap (https://projectredcap.org/software/) overall study database. In the overall study database each patient is numbered starting from 1 without the study pseudonym and the same formatting issues regarding dates which might allow to identify an individual patient (ARTORIA-study ID: 1 to XXXXX). The overall study database is based at the University of Hamburg-Eppendorf information technology department and is protected from access of other parties.

B. <u>For prospective included patients</u>

All patients still being cared of at the center visiting the outpatient clinic following placement of either a ventricular assist device or following transplantation are asked to sign an informed consent form (**supplement C – informed consent form German and English version are provided**). Additional patients presenting to the center for evaluation or listing for transplantation will be asked to sign the informed consent form.

For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety. Subjects' interests that need to be protected will not be compromised by research activity.

Following written informed consent, the personal data collected are subject to professional secrecy and the provisions of data protection law. Personal data in ARTORIA-R will be handled as identifying and non-identifying personal data. Identifying personal data, such as (but not limited to) names, complete dates of birth, place of birth, contact information and addresses will not be part of the study database and not be shared outside of the participating, enrolling study center. Here, identifying personal data is recorded in paper form and on data carriers and servers of each participating study center.

All other non-identifying study-data is stored only in a pseudonymized form. Re-identification of pseudonyms is only possible at the recruiting centers via paper or digital key lists or key databases. Only

the local principal investigators and explicitly authorized persons at each participating center have access to key lists and/or key databases which allows re-identification of pseudonyms. Reidentification may occur e. g. for proper execution of the follow-up visits.

Via pseudonymization, the actual study records which contain medical data are only identifiable via a multi-digit alphanumeric combination. Month and year of the date of birth without the exact day – which makes it non-unique – may be stored in the study database. Other identifying features are replaced to exclude or substantially complicate the identification of the study participant.

C. General aspects regarding data management and safety

Additional note on data protection and pseudonymization:

In ARTORIA-R, all data undergo a two-step pseudonymization process. First, each participating center assigns a local pseudonym before transmitting data to the national transplantation agency or registry. In a second step, the registry replaces the local code with a new study pseudonym prior to transfer to the coordinating center. This ensures that neither the registry nor the central data custodian holds any information that could directly identify individual participants. Although this process does not constitute pseudonymization in the strict legal sense (as local re-identification remains theoretically possible), it results in effectively pseudonymized data for all central analyses performed at the University Heart & Vascular Center Hamburg. The approach fully complies with the EU General Data Protection Regulation (GDPR Art. 4 §5) and the requirements of Good Clinical and Epidemiological Practice.

All pseudonymization processes are performed via software solutions written for this purpose only. Therefore, no manual touch-ups are required to pseudonymize data or to re-identify laboratory and/or genetic results. This ensures that no natural persons need direct access to key lists which could get lost or not kept under highest security standards. The software-based approach provides highest standards of data security, data privacy and data availability.

All pseudonymized study data and sample management data will be centrally stored on the server infrastructure at the core study center, the UHZ. Transfer and entering of study data will be performed via secured, end-to-end encrypted online portals hosted by the core study center. The servers and databases are protected according to highest standards and local law and measures to secure data protection, integrity and availability are implemented.

- Data protection and availability

A comprehensive safety- and backup-concept has been created to prevent data loss. All datatransferring-software will automatically create versioned backup copies of all processed data and files. The success or failure of each transfer action will be logged to allow for troubleshooting. These processes are automated.

To guarantee a maximum degree of data protection and availability, the server infrastructure hosting the database and file storage is protected by fourfold RAID-systems and mirrored on two separated servers located at different physical locations in the Geschäftsbereich IT of the UKE. An adequate data storage separated by open ground will be provided by an intermittent data backup in a data confidentiality center. All infrastructure-related measures for data availability, safety and protection are equal to those applied to patient data stored in the hospital information system of the UKE.

- User accounts, password protection, audit trails

All software components of the described infrastructure require user authentication via user accounts hosted in the identity management system of the UKE: This ensures that user accounts are disabled centrally upon leakage of account data, retirements, or other reasons for account locks. Staff members will only have access to those parts of databases which are absolutely required to perform their study related work. General access rights are restricted to the principial investigators. Besides, all software components record audit-trails which ensures authenticated documentation and versioning of all contained data and files.

- Data quality assurance

The integrity of the collected data in the databases will be controlled by detailed, predefined quality control algorithms in batches of 500 StudyIDs concerning detection of outliers, logically implausibility, or detection of mistaken identity. Certain quality control algorithms already run during data entry and notify the current user about implausible data entries. Non-valid data will be rejected at entry and rechecked manually. Only quality controlled data will be used for statistical analyses.

In the coming years the participating centers are asked to update the follow-up information of their patients using the existing pseudonym-ID or a new ID if an additional patient is entered.

Each year at 1 of July the updated Excel sheets are used to create a new ARTORIA-R database so that updated information of a patient is shown with a new ARTORIA-R study ID each year.

6. Project planning and future steps

Participation and joined publication:

National coordinator: The coordinator of each transplant society is co-shared first or senior author in one of the suggested research projects. The national coordinator did promote the project and helped in realizing the project in the country.

Local hospital/institution: The person responsible at the local hospital is named as co-author with the institution listed as well.

Future steps:

In the future additional national organ transplantation society might join the register. Especially the institutions in the United States of America, Canada for North America and the Asian countries Japan, South Korea and Taiwan in the Asia-Pacific region have a high standard of treatment and a large number of patients treated and as well support a national organ transplantation program. Thus these countries might contribute as well upon showing a working infrastructure in the geographical region of Europe.
If future projects are suggested by the institutions these are discussed in a virtual online conference including representatives of all contributing institutions, most commonly the national coordinators and the study coordinator.

Project realization:

Projects should be coordinated between the different national organ transplantation societies. In terms of future research ideas these should be communicated to the partner sites and approved by all participating sites.

Plan for dissemination and/or exploitation and dialogue with the general public or policy

Scientific results are planned to be published in peer-reviewed journals especially with the focus on cardiovascular or cardiac surgery journals. Results of the different research proposals are planned to be presented at national or international conferences. **Figure 5** shows the planned scientific and public dialogue.

Regarding the large national organ transplantation agencies cohorts of the national investigators were suggested to present the results of the national data for the register at the respective conferences on the national level.

Each of the research results on the international or national level are as well planned to be communicated with the respective patient advocacy group which are often involved in the treatment and support of campaigns to promote potential new treatment structures

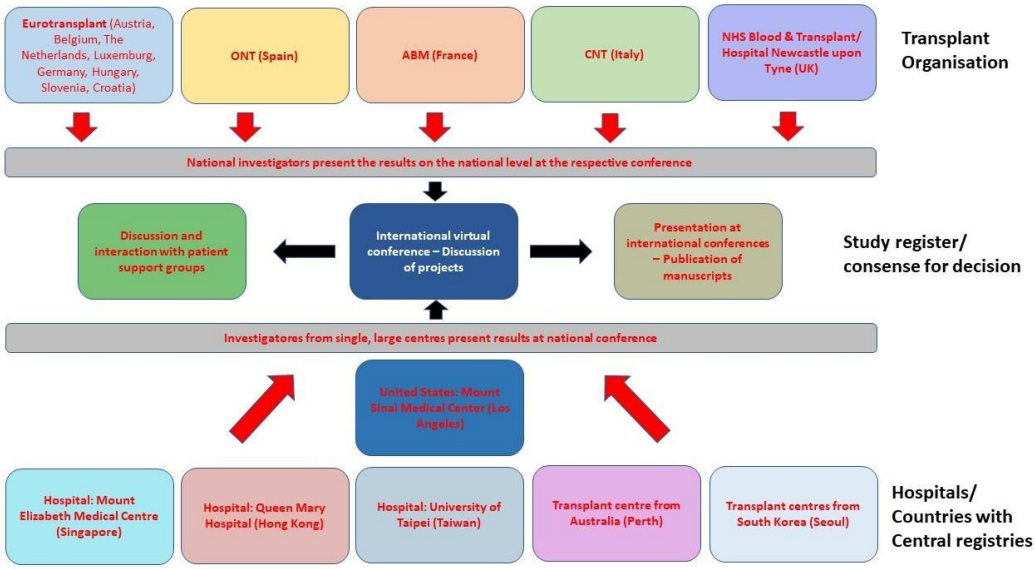

Figure 4 Scientific and public dialogue regarding the results

7. Statistical considerations

Summary statistics will be reported for continuous variables as medians (25th percentile, 75th percentile) and for binary variables as absolute counts (frequencies). Categorisation of ACHD in cohorts based on the year of evaluation or entering transplantation list is planned to assess time-dependent effects on patient characteristics and outcomes. A non-parametric Spearman test will be used to examine a potential trend over the time intervals. The null hypothesis of no trend in data will be tested for every group.

Cumulative incidence analyses will be estimated wherein heart transplantation is considered as competing risk of the primary composite endpoint death on waiting list or delisting within 5 and 10 years; and will be calculated by the Aalen-Johansen estimator for the 5/10 year follow up period. Additional endpoints will as well be evaluated with the secondary endpoint of delisting due to improvement or all-cause mortality following transplantation.

To evaluate predictors of 5-/10-year death/delisting, univariable and multivariable Cox regression models will be fitted. For the multivariable Cox regression model, variables with less clinical relevance and with missing values in >20% of the sample are not used in the models. The Cox regression models will then be weighted by the Fine and Gray estimator, which accounts for the competing risk (transplantation or death/delisting).[9]

For all regression models, change in continuous variables will be modelled as change per standard deviation to enable the comparability of variables. A two-sided *p*-value of <0.05 will be considered statistically significant. Statistical calculations will be fitted to the projects as planned and adapted if needed.

Primary outcome of the study:

- Mortality while listed or following evaluation for transplantation
- Delisting due to clinical worsening
- Delisting due to clinical improvement

Secondary outcome of the study:

- All-cause mortality following transplantation
- All-cause mortality

8. Ethical and legal aspects of the study

The current concept of the registry using pseudonymized data was approved by the ethic committee of the federal county Hamburg in Germany on 2nd September 2020 (file reference WF163-20). The study has been reviewed, in individual countries, in line with national requirements for ethical approval and followed according to local protocols for data management. The study complies with the current General Data Protection Regulation in Europe enacted on May 23 2018.

1. Ethical and legal aspects

    1.1. Good clinical and epidemiological practice

The procedures set out in this study, pertaining to the conduct, evaluation, and documentation, are designed to ensure that all persons involved in the study abide by Good Clinical Practice (GCP), Good Epidemiological Practice (GEP) and the ethical principles described in the current revision of the Declaration of Helsinki. The study will be carried out in keeping with local legal and regulatory requirements. The requirements of the GCP and GEP regulation, and the General Data Protection Regulation (GDPR) of the European Union will be kept for all study centers in Europe including the UHZ. Centers outside of the European Union are not obligated to follow the GDPR but will be reviewed, in individual countries, in line with national requirements for ethical approval and followed according to local protocols for data management. All data will be combined in pseudonymized fashion at the data custodian institution (University Heart & Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany).

1.2. Confidentiality

The name of the subjects and other confidential information are subject to medical professional secrecy. All members of the study staff are obliged to maintain confidentiality of all collected data. Obligations to maintain confidentiality comply to the principles of the General Data Protection Regulation (GDPR) in those study centers residing within the European Union. In all other institutions, local regulations regarding data management and ethical regulations apply. Personally, identifying information will never be shared outside the study center (except for month and year, not exact day of birth; cf. chapter 8).

1.3. Subject information and informed consent

Before being admitted to the observational study, the subject must consent to participate after the nature and scope of the study have been explained in a form understandable to him or her. The subject must give consent in writing.

A copy of the signed informed consent document must be given to the subject. The documents must be in a language understandable to the subject and must specify who informed and consented the subject.

1.4. Procedure in case of withdrawal of the written informed consent

In case that a study participant withdraws her/his written consent or decides to end the study participation prematurely. Furthermore, an entry will be made into all study-related databases which indicates the withdrawal of consent and premature study end of the specified subject. With the end of the data recruitment phase all personal identifying data of this person will be deleted in the study management database. The pseudonymized study data will remain in the study data base and can be further analyzed.

1.5. Responsibilities of the study staff

All participating centers should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, and their study-related duties and functions. The center should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

1.6. Approval of the study protocol and amendments

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC). Formal approval by the EC should preferably mention the title of the study, the study code, the study site, and any other documents reviewed. Further, it must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

2. Quality assurance

This study will be conducted according to the principles of Good Clinical and Epidemiological Practice (GCP, GEP). An initiation meeting will be held prior to study start to discuss the protocol, laboratory procedures and to provide an opportunity for the study staff to ask any questions prior to screening patients. The concept of quality assurance for the project contains an internal quality control.
For internal control a permanent data validation of the remote data entry into the study's database is performed. All data are checked for plausibility automatically. Non-valid data will be rejected at entry and re-checked manually.
Automatized periodical quality controls are performed by data management to detect changes in data quality and to check data for correctness, completeness, representativeness, and accuracy. The results are analyzed and compared with previous results. Any changes in the study database are documented. If the database is amended a new value, the old value is kept for documentation.

9. Study organization

Study management board

The study management board is responsible for the conduction of ASTRA-AF INTERNATIONAL true to protocol at the participating study centers. The study management board suggests the guidelines for the ASTRA-AF INTERNATIONAL study and is assigned with the direct organization and implementation of the study as well as the guidance of the study at the participating centers.

Members of the study management board are the principal investigators of ARTORIA-R, as well as an individual physician of each participating center. The study management board meets at least every 4 months by means of a virtual online conference to discuss the next steps.

10. Publication

Any publication in any form will require the commitment in a majority decision of the study management board. For each proposed publication, a proposal must be sent to the study management board. Approval of research proposal is given by the study management board unanimously. After approval of a research proposal, requested data will be transferred to the respective partner site. The publication has to be sent for approval to the study management board before submission. The study management board may request disclosure of all raw data, interim analysis data and analysis steps in order to comprehend presented results.

Pseudonymized, aggregated data will be published in peer-reviewed journals, book chapters, as part of theses (i.e., doctoral, habilitation), reviews, scientific journals. Patients are informed regarding the use of pseudonymized data for scientific publications. No identifying data will be published.

11.Signatures

Study Coordinator
PD Dr.med. C. Sinning

Name

Date

Principal Investigator
Prof. Dr.med. P. Kirchhof

Name

Date

Principal investigator
Prof. Dr.med. Dr.phil. H. Reichenspurner

Name

Date

Principal investigator
Prof. Dr.med. S. Blankenberg

Name

Date

Principal investigator
Prof. Dr.med. Michael Hübler

Name

Date

Statistician Dr. Francisco Ojeda

Name

Date

12.Literature

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Addendum 1 – Two-Step Pseudonymization Process

In ARTORIA-R, all data undergo a two-step pseudonymization process. First, each participating center assigns a local pseudonym before transmitting data to the national transplantation agency or registry. In a second step, the registry replaces the local code with a new study pseudonym prior to transfer to the coordinating center. This ensures that neither the registry nor the central data custodian holds any information that could directly identify individual participants. Although this process does not constitute pseudonymization in the strict legal sense (as local re-identification remains theoretically possible), it results in effectively pseudonymized data for all central analyses performed at the University Heart & Vascular Center Hamburg. The approach fully complies with the EU General Data Protection Regulation (GDPR Art. 4 §5) and the requirements of Good Clinical and Epidemiological Practice.