Aortic Valve Replacement using Individualised Regenerative Allografts:
Bridging the Therapeutic Gap

European Union's Horizon 2020 Research and Innovation Programme
Call: H2020-PHC-2014-single-stage
Contract No: 643597

Ethics and Governance Framework

Deliverable No: D2.2

Version 1.1

Project acronym:	ARISE
Project full title:	Aortic Valve Replacement using Individualised Regenerative Allografts: Bridging the Therapeutic Gap
Work Package:	WP2: Ethics and Governance
Lead beneficiary:	LUH

Document title:	Ethics and Governance Framework
Version:	1.1
Official delivery date:	31.03.2016
Actual publication date:	31.03.2016
Type of document:	R: Report
Status:	final
Dissemination level:	public
Person month in WP:	24

Authors: Beier, Davies, Eklu-Natey, Grewal, Hoppe, Jystad, Robienski

Document History

Version	Date	Author/Editor	Description/Comments
1.0	2016-03-31	Beier, Davies, Eklu-Natey, Grewal, Hoppe, Jystad, Robienski	
1.1	2016-03-31	Di Dio	Editing

Content

1 Introduction

This is the Ethics and Governance Framework (EGF) of two EU-funded projects seeking to test decellularized heart valves: ARISE and ESPOIR. The EGF expresses the values and principles which the partners in these projects undertake to adhere to. It is a living document and subject to regular revision and evolution, based on discussions within the project and the Ethics and Governance Council (EGC).

1.1 Description of the EGC

(1) Notwithstanding its structural position within the two projects, the EGC operates independently of ARISE and ESPOIR.

(2) The remit of the EGC includes: (a) acting as an independent guardian of the EGF; advising the projects' consortia, the projects' steering or management groups on revisions, monitoring and public reporting of this EGF as well as project compliance; providing overarching advice concerning participant interests, as well as those of the general public.

(3) The EGC will engage with a number of internal and external audiences. Internal dialogues will be with the management groups and the consortium partners. External dialogues will be with participants, regulatory or government bodies, other interested parties, and the general public. The EGC does not speak on behalf of the projects; instead it will speak about the projects.

(4) In order to fulfil its responsibilities, the EGC will need to be informed about the projects' activities. Effective communication will occur on the basis of mutual respect and cooperation. Where necessary, the EGC will request the necessary information from partners, and initiate relevant discussion.

(5) The EGC will communicate its reflections and feedback in an informal manner. The EGC may, if it considers it appropriate, release a formal statement of concern or, if necessary, a public statement concerning. Ultimately, members of the EGC may choose to resign and make a public announcement to this effect, giving reasons.

(6) The EGC will work in an open and transparent manner, reporting to participants and the wider public. This may be achieved in various ways, such as through publishing reports of its reviews or discussions, occasionally meeting in public, or holding meetings with the public.

1.2 Information about the Project

The scope of the proposed work in the projects has changed after regulatory approval for the decellularized allogenic heart valve matrices (DAH) was obtained by the German regulator, the Paul-Ehrlich-Institute (PEI). PEI approved the use of DAH under s. 21 AMG (the German Medicinal Products Act). This means that the clinical, and specifically the surgical, aspects of the use of DAH are under the umbrella of standard clinical practice, and clinical ethics and not within the remit of the EGC.

1.3 The Observational Study

(1) The successful approval of the DAH has led to a number of changes:

- an aortic valve replacement using a DAH is now considered to be a conventional medical treatment for regulatory purposes;
- the projects' work therefore does not cause additional surgical interventions, but merely observes the success of a conventional intervention;
- therefore only patients' medical records and data will be monitored and evaluated;
- the planned clinical trial has become a non-interventional, observational study (cf. s.. 2(23) 2 AMG);
- minors have now been included in the observational study; and
- patients who have received a DAH during the course of transplantation surgery may also be included in the study.

(2) The German regulatory approval, and the associated consequences, apply to all participating centres in these projects. Additionally, in Germany, both the DAV and the surgery are reimbursed by the (statutory) health insurance.

(3) The data gathered and produced in the projects will be stored securely, and are used to fulfil any documentation obligations (e.g. s. 63 I AMG), and may be used (in appropriate circumstances) for related secondary research.

1.4 Introduction to the EGF

(1) Living Document: The EGF is intended as a living and evolving document, which articulates the values, structures and procedures for the projects. It will likely change on the basis of experiences from the projects, and feedback from stakeholders.

(2) Guidance and not legal advice: The EGF aims to establish conditions for good governance and virtuous operation but cannot replace legal advice or local ethics committee approvals. Compliance with the EGF fosters trust with participants and the wider public, but does not mean that partners have fulfilled all of their respective regulatory obligations.

(3) Implementation: The implementation of the provisions of EGF is the responsibility of the Project Coordinators, the management groups, and the Data and Safety Monitoring Board (DSMB), if any.

2 Main Principles

2.1 Gift / donation

The projects exclusively use self-acquired homografts with clear and well-documented provenance. Homografts from unknown sources will under no circumstances be accepted for decellularization. The project participants acknowledge that a homograft is an altruistic gift, and will treat the gift with respect and care, and will ensure that all use of the gift is in accordance with the principles of altruistic donation.

2.2 Local Laws and Ethical Guidelines

(1) All treatment and research within the projects will at all times comply with local laws, and the stipulations of local ethics committee approvals, if any.

(2) Treatment and research will also comply with key European and international regulatory frameworks, and ethical guidelines, namely:

- Directive 2001/20/EC of the European Parliament and of the Council;
- Directive 2005/28/EC of the European Parliament and of the Council;
- WMA Declaration of Helsinki: Ethical principles for medical research involving human subjects, 2013
- The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, 1997
- Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research, 2005 ;
- Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin, 2002: and
- WMA Ethical Guidelines, i.e. Declaration on Ethical Considerations regarding Health Databases and Biobanks.

(3) In case of conflict, priority is given to law. Whenever possible, the law should be interpreted in a manner that takes ethical guidelines into account. The EGC advises partners in cases of conflict, but cannot replace appropriate legal advice.

2.3 Patients' Best Interest

Researchers and physicians must not put donors, research participants, or patients at undue risk. Researchers and physicians should be motivated by beneficence (an ambition to actively do good) and non-maleficence (a will to do no harm), thereby avoiding unnecessary risks, managing acceptable risks, and ultimately improving the quality of life of patients.

2.4 Allocation of Scarce Resources

(1) Allocation decisions are clinical decisions. These decisions will be made based on the spirit of the EGF, which promotes transparency and fairness. The EGC and the projects will pursue the issue of allocation as a specific dialogue to be had during the course of the projects.

(2) In case non-project funding is available for the reimbursement of costs, the project partners undertake to reallocate project funds to those partners who are unable to seek alternative reimbursements.

2.5 Dignity, Self-Determination

(1) The project partners recognise the importance of humanity and respect for individuals (including their vulnerabilities and potentialities). They acknowledge the need to balance the imperative to conduct research with other fundamental values, such as dignity and self-determination, and undertake to never exploit individuals.

(2) The project partners understand the desire of individuals to exercise free will and the significance of providing a space within which individuals can make decisions about and for themselves according to their own values and desires. This means that patients are given adequate information in a comprehensive manner so they are able to make informed choices, and be satisfied that reasonable steps will be taken to protect their personal information.

3 Consent and Autonomy

3.1 Main Principles

(1) Seeking informed consent is paramount in medical research involving patients. Consent is only lawful and valid when patients have the capacity to decide whether to take part in the clinical trial, have been properly informed, and have agreed to participate without pressure or coercion. The project partners are aware, respectively, of their domestic legal obligations in relation to seeking, obtaining and documenting consent.

(2) Patients give their consent in writing. It is a legal requirement to obtain appropriately documented consent from patients participating in clinical trials involving investigational medicinal products. The responsible physician will confirm that a valid written informed consent has been obtained immediately prior to the provision of medical treatment during the clinical trial.

(3) Patients will be given an appropriate time span to make decisions in relation to their participation in the projects.

(4) Patients are not pressured or coerced into consenting to participate in the clinical trial in the expectation of therapeutic, financial or any other benefit.

3.2 Responsibility for seeking consent

(1) Patients who are selected for potential inclusion in the study should only be approached, informed and consent should be sought by an individual who is independent of the projects. This individual must have full knowledge of the proposed research, including what the study will involve and any anticipated benefits and foreseeable risks.

(2) Consent for clinical intervention outside of the projects must be obtained by the responsible physician, who is performing the specific medical intervention. The project partners undertake to ensure that this is the case for all patients who are included in the study.

(3) In the event that this responsibility is delegated to someone else, the responsible physician must ensure that the individual has sufficient understanding of the clinical trial and the specific medical intervention, as well as the appropriate skills and competence to seek consent.

3.3 Information

(1) Patients must be provided with information they need and wish to have in order to decide whether to take part in the clinical trial. The level of information provided will depend on patient's individual circumstances.

(2) No assumptions must be made about the information a patient might want or need, their level of knowledge, as well as their understanding of the proposed clinical trial. The project partners undertake to treat the consent process as an individualised dialogue with the patient.

(3) The fundamental information required by patients must be included in the participant information sheet, which in turn ought to regularly be updated to reflect the learning generated in the projects.

(4) Any further information requested by patients should be provided. This may include a copy of the protocol approved by a research ethics committee. Patients must be provided with details of an independent person or organisation which is at the patient's disposal in case they require further information or wish to discuss the research project. Patients must be provided with the contact details of a responsible individual to whom they can address concerns, especially if they wish to withdraw from the respective project.

(5) The key elements of the discussion with patients relating to their decision to take part in the clinical trial must be documented.

3.4 Right to withdraw

(1) The project partners, with the assistance of the EGC, will develop a protocol for the withdrawal of consent, and subsequent deletion of patient data, etc.

(2) Patients must be informed of their right to decline to take part in the research study, and to withdraw from the clinical trial at any time.

(3) Patients must be informed if the treatment options available to them may be affected by their decision to withdraw from the treatment in the clinical trial.

(4) It must be ensured that their decision will not adversely affect their relationship with those providing medical care or the medical care they receive.

(5) Patients' right to decline to take part in the clinical trial and to withdraw from the clinical trial must be respected by everybody.

(6) Patients must be informed that the possibilities to withdraw from data usage are limited once the data have been used for research.

3.5 The Provision of Comprehensive Information

(1) Patients must be given information in a way that they can understand.

(2) It must be ensured that patients understand terminology and any explanation relating to the research study, the medical treatment and associated risks.

(3) Comprehensive and accurate written material or visual or other aids (such as the website of ARISE and ESPOIR) should be provided in addition to the discussion with the patient.

(4) Arrangements must be made to accommodate the patient's language requirements, communication and other support needs, for example by way of translations of pertinent documents, or the use of an interpreter where appropriate.

(5) Patients who require additional assistance shall not be excluded from the clinical trial and other benefits that the medical treatment in the research study can offer them. Reasonable adjustments should be made by the projects to accommodate such patients.

3.6 Information sheet

(1) The information and consent documentation must be transparent and easily comprehensible. The forms should, whenever possible, not exceed two pages. The documentation should be available in different languages. The content of the information documentation should be limited to the key aspects of the research study.

(2) Further sources of information should be made available in written form for the patients who are in the need of more detailed information. Whilst a helpful starting point, it is not sufficient to refer patients to internet sources. Consideration must be given to the fact that some patients may not have access to, or sufficient working knowledge of, internet resources.

(3) The subjective and individual situation of each patient must be taken into account while designing all relevant forms and sheets. Advantages, disadvantages, risks and benefits should therefore be presented in a well-balanced, transparent and open manner.

(4) The documentation should be designed in a consistent manner in every participating clinic. Individual adjustments should only be made where domestic law requires these

changes, and ought to be subject of discussion within the consortium and, if appropriate, with the EGC.

3.7 Secondary Research and Re-Contacting Patients

(1) The experiences and results of the projects may be an important resource for further research in various fields (including, but not limited to, tissue engineering).

(2) Patients will be asked for written consent to participate in future research projects, and for secondary use of their data.

(3) There may be occasions when further or additional consent will be sought, such as when proposed activities clearly fall outside the scope of the patient's prevailing consent. Donors may need to be re-contacted by the projects for various reasons, including but not limited to the following situations:

- to collect additional information (such as questionnaire data, measures for research);
- to seek consent for inclusion of the patient's health record and data in new uses that have passed scientific and ethics review, but that do not fall within the existing consent; and

(4) Participation in all activities necessitating re-contact is entirely voluntary, and any initial re-contact will be undertaken by the projects, rather than secondary researchers who may have expressed a wish to use the projects' data.

(5) Decisions about whether re-contact is warranted will be made by the projects' management groups, with advice from the EGC, and will where appropriate be subject to Research Ethics Committee approval.

3.8 Children and Young People (Minors)

(1) Including minors in the projects can particularly benefit children with heart valve disease. A significant level of vulnerability exists in relation to minors. They are not always capable of acting in their best interests, expressing their needs or defending their rights.

(2) Where a minor is involved in research, consent must be obtained from both parents where possible, particularly if the research involves risk that is greater than low or minimal harm. If a patient is under 16 years of age, assent or consent must be obtained from them if they otherwise have capacity to make decisions. Parents should give their consent even if a minor under the age of 16 is able to express consent for herself/ himself.

(3) Minors, as well as their parents, must not be pressured or coerced into consenting to participate in the clinical trial in the expectation of therapeutic, financial or any other benefit.

(4) Minors should not be included in the research study if they refuse or appear to refuse in either words or actions, even if parents have given their consent.

(5) Minors must be informed about the projects in an age-appropriate manner.

(6) If a minor lacks the capacity to make a decision with regards to participation at the beginning of the project, the minor should be asked for consent when she/he has gained the necessary capacity to make such a decision.

(7) Minors should be re-contacted at the [age of 16] to refresh their consent unless local law requires earlier re-contact.

(8) When re-contacted, the patient should receive all information about the project, the data that has been used and her or his possibilities to withdraw from further data usage.

3.9 Data Protection / Data Security

(1) A wide variety of measures have to be taken to ensure the security of data, samples, the database and the information technology system in general. These should include staff training and confidentiality assurances, physical and electronic controls on access to data, cyber security, and physical security. This should prevent identifiable information from being used – inadvertently or deliberately – for any purpose other than approved research.

(2) Patients must be informed about all aspects of data storage, namely the length and mode of storage; data use and data coding.

3.10 Right to Know / Not to Know

(1) The patients ‘right to know' and the corresponding 'right not to know’ are fundamental and must be respected by any partner, physician, or individual involved within the projects.

(2) Patients must be informed about these rights, and appropriate protocols must be in place to ensure that information flow to patients reflects these rights.

4 Communication and Information

4.1 Reporting

(1) Patients as well as the public have the right to know the scope and purpose of the research study, its risks, benefits and expectations, researcher conflicts, and the provenance of material sources. Researchers and physicians should be expected to be called upon to defend and/or explain their work, and they should be expected to record and make their work public.

(2) Patients should have access to all relevant publications and news/developments concerning the project. Although publications are open access, the projects should provide centralised access to the patients by establishing a patients’ intranet giving access to all relevant publications and news/developments. This intranet may also serve as a platform for exchange between patients and physicians.

(3) Patients who do not have access to the internet should have a centralised contact point that will ensure that relevant documents are sent to the patients in an appropriate format.

4.2 Incidental Findings / Adverse Incidents

(1) Feeding back information about incidental findings or adverse incidents is primarily the responsibility of the treating physician in the context of medical treatment and not of researchers within the project.

(2) Individual adverse incidents must be reported to the local competent authorities in any event.

4.3 Confidentiality

(1) The projects are committed to protecting the confidentiality of data and samples. Systems will be in place to secure data flow and to protect confidentiality, (reversibly) anonymise data, and enforce security. These measures will be explained to participants during the consent process.

(2) With the patient’s consent, the patient’s family doctor, as well as other clinicians responsible for the patients' care must be informed about the patients' involvement in the research study and about any other information necessary for the patient’s continuing care.

(3) If a patient refuses information being shared in this way, the potential consequences of not sharing information must be explained to them. If the patient continues to refuse, their wishes must be respected, unless sharing the information is justified in the public interest, or required by law.

4.4 Monitoring

Participating clinics are expected to provide all relevant forms, documentation, and other information to the EGC upon request.

5 Financial / Commercial Interests

5.1 Conflicts of Interest

(1) The projects establish written policies and procedures to identify, manage, and minimise or eliminate financial conflicts of interest that could influence the conduct or the integrity of the research studies.

(2) The projects should follow written policies and procedures to identify, manage, and minimise or eliminate individual financial conflicts of interest of all project partners, physicians, researchers, staff and their immediate family members, that may influence the conduct or the integrity of the research studies. The projects should also work with

the EGC and the appropriate local ethics committees in ensuring that financial conflicts of interest are managed and minimised or eliminated, when appropriate.

(3) Individuals working within the projects should submit a *Conflict of Interest Declaration* to the project management, and to the EGC to reveal any of the following financial interests related to the research study:

- Financial interests (e.g. stocks, stock options or other ownership interests) in the assets or liabilities of any company that may benefit from the research activity;
- Payments (e.g. salary, consultation fees, speaking fees, or honoraria) from any company that may benefit from the research activity;
- Employment or executive relationships with any company that may benefit from the research activity.
- Intellectual property rights or proprietary interests (e.g. patents, copyrights and royalties from such rights) related to the research; and
- Options or other compensation arrangements that could be affected by the outcome of the research.
- The declaration should give full disclosure of the facts giving rise to the financial interest and to detail the steps proposed to eliminate any conflict of interest that arises from the financial interest.

(4) Financial conflict of interests may also arise during the lifetime of the study. If such interests arise, the investigator and/or affected consortium member should submit an updated Financial Conflict of Interest Declaration as soon as possible but not later than **30 calendar days** following first knowledge of these conflicting interests.

(5) The project management, supported by the EGC, will review the disclosed financial interests to determine their impact on the integrity of the research and that the management plan to eliminate any conflict of interest is appropriate.

5.2 Intellectual Property

[For subsequent discussion in the EGC]

6 Benefit Sharing

The projects acknowledge the need to justly share the benefits of research and undertake to engage with the EGC to establish models for benefit sharing, and transparent communication protocols for communicating benefit sharing activities.

7 EGC

7.1 Approachability

Any project partner, patient, or other stakeholder may approach the EGC with issues of concern, or requests for guidance (by e-mail: arise@cells.uni-hannover.de, or by telephone: +49 511 762 5222). The EGC undertakes to discuss and respond to reasonable requests for information within an appropriate time.

7.2 Project as a partner

(1) The EGC seeks to enable the discussion and evolution of guiding principles with the projects. It provides a common principle basis for all participants, partners, and stakeholders. It is a critical friend to the project.

(2) The EGC aims to support the consortium members internally, and undertake appropriate communication externally.

(3) By the means of the EGC, the projects establish an internal partner who can assist with external assessments and horizon scanning.