ESPOIR Report Summary

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Final Report Summary - ESPOIR (European clinical study for the application of regenerative heart valves)

Executive Summary:
December 2016 saw the closing meeting of the ESPOIR project held in Zurich. Within the 5-year lifetime of the project, researchers across Europe have worked towards the dissemination and uptake of the promising technology of decellularising human heart valves prior to implantation as replacement for a malfunctioning pulmonary valve. This concept reduces the immunogenicity of the implanted heart valve as less antigens deriving from the donor are present. It also facilitates recellularisation by recipient cells, thereby holding the potential for regeneration and preservation of the matrix functional structure. An independent Ethics and Governance Council, including members from patient organisations, supervised and advised the project, in addition to the monitoring procedures mandated by national legal requirements and the approval by local ethics committees prior to start of the clinical study.

In the initial phase of the project, which lasted almost three years, corlife oHG, a spin-off of Hannover Medical School, took forward the approval process of the decellularized heart valve and the setup of the study with the competent authorities and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®). In this context, the ESPOIR study took on a pioneering role, as it was the first time that the authorities in all of the participating countries had been faced with the combination of regulatory approval for a decellularized human heart valve, cross-border shipment of human tissue preparations, and the approval of a study testing such preparations. Heart valve decellularisation can now be provided by corlife oHG to any interested tissue bank or hospital fulfilling the European Directives on tissue donation. Reimbursement for this processing service already has been granted by the health insurance systems in Germany, Austria, and Switzerland and is based on a uniform processing fee.

After approval of ESPOIR PV, the clinical trial started (8/2014) in the setting of a so-called non-interventional trial, which means that the heart valve was implanted according current guidelines and according its authorisation following surgical indication for a decellularised heart valve.

Within two years, 121 patients were included in the controlled prospective clinical trial at 7 clinical centres within Europe. Together with the clinical centers, 4 leading Tissue Banks (European Homograft Bank (BE), Deutsche Gesellschaft für Gewebetransplantation (DE), Fondazione Banca dei Tessuti di Treviso (IT) and Euro Heart Valve Bank (NL)) closely collaborated within the ESPOIR project to procure human heart valves, which were sent for decellularisation to Corlife oHG. Figure 1 shows an overview of the project's consortium and their location in Europe.

After allocation of the processed heart valve by the procuring Tissue Bank to a specified recipient at one of the clinical centers, the processed heart valves were implanted using standard surgical procedures. ESPOIR PV implantation has proven to be safe and simple; no adverse events relating to the mechanical stability of the decellularized matrix structure occurred. The ESPOIR investigators will report on their early experiences with the decellularized valve in comparison to matched contemporary cohorts within the participating hospitals in 2017.
The study is flanked by the ESPOIR Registry, which includes the data of all patients who have received a ‘decellularized human pulmonary valve, Espoir PV’ both, within or outside of the ESPOIR clinical study over a period of at least 10-years. This will allow robust assessment of decellularised heart valves for pulmonary valve replacement, including but not limited to diameter development and regenerative capability. The ESPOIR Registry to date comprises data of 240 patients and evidences extraordinary results in terms of freedom from explantation at 99 % since 2005.

Project Context and Objectives:

Cardiovascular diseases (CVD) affect the heart and the blood vessels and can take many forms, such as high blood pressure, coronary artery disease, heart valve disease and stroke. At present, cardiovascular diseases represent the most significant cause of death in the EU. Congenital heart defects, which occur in one out of one hundred newborns in the EU, are a major contributor to heart valve disease. The scale of the resulting socio-economic burden is evident if we consider that 5 million people in the EU are currently living with congenital heart defects with the resulting total financial burden estimated about 169 billion €uro per year.

Both acquired and congenital heart disease can require heart valve replacement. Currently available heart valve substitutes are, however, not ideal as they require anticoagulation, with the risk of bleeding when manufactured from non-organic material, or they degenerate when derived from animals (xenografts) or human tissue donors (homografts), leading to the need for frequent reoperation, especially in children and young adults. An ideal heart valve substitute would have the potential to grow even when implanted in pediatric patients.

In recent years, research has increasingly focused on regenerative biology and reconstructive therapies in cardiovascular diseases. The field of tissue processing has emerged as an alternative in search for an ideal valvular graft that could overcome the limitations mentioned above, based on the principle of in vitro and/or in vivo repopulation of biological scaffolds with autologous cells.

Decellularized human heart valves (DHV) - a novel regenerative approach:

Haverich et al. (Partner 1 of the ESPOIR consortium, Hannover Medical School) have developed a novel implant for heart valves, which is better tolerated than the known alternatives and which has potential for regeneration. Implants derive from donated, non-cryopreserved, human heart valves (homografts), which are chemically treated to inactivate adhering microorganisms and viruses. The heart valves then are decellularized chemically, so that only connective tissue remains, the heart valve matrix (DHV). DHV is stable and can be stored and shipped. It has been examined in extensive animal studies, including immunological and toxicological analysis, which have shown that the implant is well tolerated and recellularized by the recipient.

Starting in 2002, Haverich et al. were one of the first research teams to report clinical application of tissue engineered heart valves in pediatric patients. Initially DHV was applied in combination with seeding of autologous progenitor cells and growth of the DHV was demonstrated. Active seeding became unnecessary as spontaneous re-endothelialization of DHV by circulating endothelial progenitor cells was observed. Since then non-seeded, decellularized heart valves (DHV) have been used throughout.

Before the start of the ESPOIR project, 45 children and young adults had already been treated with these valves in Chişinău (Moldova) and Hannover (Germany). Although these represented early clinical results only, none of these valves needed to be explanted due to degeneration or rejection, and immunological follow up revealed no abnormalities in these patients. Moreover, a near physiological development of valve diameters was observed.

The main objective of the ESPOIR project was translation of the innovative regenerative therapy presented by the DHV regenerative heart valve into widespread clinical use. To achieve this goal, the ESPOIR consortium worked on:
1. Evaluating DHV for pulmonary valve replacement rates in direct comparison to current heart valve substitutes such as cryopreserved homografts and xenografts within a large prospective multicentre trial at 7 leading European Centres for Congenital Cardiothoracic Surgery. 121 patients could be included to the ESPOIR clinical trial. In addition, 119 patients having received DHV for pulmonary valve replacement prior or outside the ESPOIR project were included into the ESPOIR Registry, which is following all DHV patients for robust statistical analysis regarding re-operation and re-intervention rates, hemodynamic performance, growth potential and long term durability. Follow up structures for patients were implemented with the ESPOIR project to obtain long term results of DHV.

2. Establishing sustained structures for European-wide homograft procurement with special emphasis on small homograft sizes thereby facilitating increased definitive primary repair in congenital heart defects.

3. Disseminating the results of ESPOIR to the scientific community, patient organisations and political stakeholders.

4. Implementing exploitation structures of the decellularization technique in collaboration with homograft banks and national health insurance systems.

Project Results:
WP 1 Project Management and Governance

Work package objectives

• To ensure the effective and timely planning, steering and coordination of work, tasks and outcomes of the individual work packages and the project as a whole.
• To provide the necessary structures and support to facilitate project management, decision-making, quality management and accountability.
• The administration and financial management of the project, including the periodic and final reports to the EU Commission.
• Communications and liaison with external groups and with the EU Commission.
• EGC Meetings.
• Establishment of an external Ethics and Governance Council to
  a) Provide ethics monitoring, counselling and advice.
  b) Provide external scientific expertise via a world-renowned expert in cardiothoracic surgery.

Main results

Regular formal and informal meetings have taken place throughout the project. Six Steering Committee Meetings were held throughout the projects runtime and offered a platform for the project partners to discuss the development of the project, eventual difficulties, first results and administrative matters. The USER-M project management office of the Leibniz University of Hannover (partner 12) established effective internal reporting structures to facilitate project controlling by eliciting biannual reports on activities and expended resources from all partners. Communication infrastructure to support regular exchange between partners and work packages and with the project’s contact persons at the European Commission was set up. The project’s specific quality management handbook was made available to all partners and guidelines were updated on a regular basis and distributed to the consortium. The payments were distributed among all partners by the coordinator directly upon receipt and support has been continuously provided for project partners throughout the reporting period in all project-related financial and administrative matters, including the preparation of the current periodic report. Administrative challenges like the extension of the project’s runtime, legal changes and budget shifts were coped with effectively to ensure the achievement of the project’s objectives. Throughout the whole project’s lifetime there was close communication with the Project Officer and the Financial Officers to provide
updated information on the project progress via telephone and e-mail in addition to the interim reporting. The project coordinator also has maintained regular contact with the Ethics and Governance Council (EGC) to update them regarding project events and progress and an Ethics and Governance Framework (EGF) for the projects ESPOIR and ARISE was developed. The EGF offers advice and recommendations regarding ethical issues like informed consent, allocation and reimbursement.

WP 2 Procurement of Homografts

Work package objectives

- The harmonization of safety and quality standards of donated tissues via a uniform protocol for all participants.
- The supply of homografts for processing and implantation as well establishment of a clinical procurement program for heart-beating donors (HBD) via “domino-principle”.
- Development of a procurement program for post mortem donors (PMD).
- Partnership with clinical partners to ensure sustainability beyond the duration of ESPOIR.

Main results

The activities of heart valve allocation during the project ESPOIR were handed to the two tissue banks European Homograft Bank (EHB - partner 11) and Deutsche Gesellschaft für Gewebetransplantation (DGFG – partner 10). Tissue banks are a form of procurement organisation and are traditionally responsible for allocation of donated and (in the case of the ESPOIR study) processed tissue. Procurement organisations are mostly non-profit organizations, which have committed themselves to a fair and transparent distribution of tissue donations.

To enable a homogenous valve supply process, EHB and DGFG worked on the harmonization of quality and safety standards of donated tissues via a uniform protocol for all participants. The different quality management systems of both banks, concerning the medical reasons for donor exclusion as well as quality standards for pulmonary valve acceptance, were discussed and a common protocol for heart beating donors and post-mortem donors was developed.

Both tissue banks worked in close collaboration with corlife (partner 9). A clear definition of responsibilities between DGFG and EHB as well as between DGFG/EHB and corlife had to be worked out several contract regarding the supply of valves were established.

During the course of the project the allocation of heart valves proved as one of the major challenges for ESPOIR. Internal structures and national law of some EU member states, especially the countries beyond the EBH/DGFG network, were stricter than the requirements of the relevant EU-Directives. Some countries imposed special or additional requirements on the import of the heart valves. Cross-border allocation of tissues turned out as complicated and time consuming issue. The originally consented idea of a common homograft pool shared by all involved EU countries was modified towards a more or less bilateral structure.

Throughout the whole project representatives of EHB, DGFG, corlife and the clinical centres of the consortium got into touch with local tissue banks, in order to expand the pool of valve supplying organisations and to establish long-term partnership and ensure sustainability beyond the duration of ESPOIR. Until the end of the project two more tissue banks joined the network to supply tissue for the ESPOIR clinical trial: the Fondazione Banca dei Tessuti di Treviso (Italy) and the Euro Heart Valve Bank (Netherlands).

Tissue donation via post mortem donation (PMD) turned out as another challenge for the procurement process. While tissue donation via PMD is common in Belgium, the situation in Germany is reversed. Infrastructure had to be established at DGFG first. Clinical rooms were audited and the training of staff took place. After a long preparation phase the first-ever post mortem donation within the DGFG was performed in coordination with and monitored by MHH (partner 1). A base to accomplish the future establishment of a procurement program with post mortem donors was built. During the project’s runtime valves from PMD were only supplied by EHB.

Through the continuous commitment and effort of the participating homograft banks Corlife received a total of 158 pulmonary
heart valves for decellularisation during the ESPOIR project. (European Homograft Bank 29 %, Deutsche Gesellschaft für
Gewebetransplantation 46 %, Fondazione Banca dei Tessuti di Treviso 10 %, Euro Heart Valve Bank (12 %) and AKH Vienna 3
%).

Possibilities for reimbursement of decellularized heart valves in different countries were discussed and dialogue regarding the
advantages of the technology was initiated with scientific and politic stakeholders. Until the end of the project the arguments
convinced the health insurance companies in Austria, Germany and Switzerland. Further study results will help the DHV to be
recognized as an affordable therapy.

WP3 Processing

Work package objectives

• To supply DHV for implantation from HBD-specimens as well as from PMD-specimens.
• To ensure sustainability beyond ESPOIR, the processing of homografts shall be established at other sites, e.g. at homograft
banks on the models of strategic partnerships.
• To cooperate closely with WP 4 for synchronization of processing and surgical implantation.

Main results

Throughout the project ESPOIR the company corlife (partner 9) was responsible for the decellularisation process of the
pulmonary heart valves. Preconditions for the production of decellularized heart valves are the approval of the production
facility and the approval of the product.

Corlife oHG was admitted as a tissue establishment according to Directive 2004/23/EC that may accept human tissue for
processing and storage during the second year of the project’s runtime. For the approval of the decellularized valves as a
product, a Standard Operating Procedure (SOP) for the processing of tissues from living and dead donors was established by
corlife. The SOP is part of a detailed documentation, the so-called Common Technical Document (CTD), and was evaluated by
the German competent authorities Paul-Ehrlich-Institute (PEI). On the one hand, the CTD comprises the use of tissue, labeling
and quality assurance. On the other hand it contains a detailed description on the processing of the valves. The pulmonary
valve, ESPOIR PV, was approved as a safe product for the use in surgery by PEI during the second year of the project as well.
The approval of the product by PEI turned out as another challenge for the consortium, which consumed a lot of time and
caused a rescheduling of the project’s work plan. The processing had to start far later than expected and reduced the time
frame available for the decellularisation process throughout the project.
The tissue is sent to corlife in standardized dispatch units, which are provided by corlife. Different test regarding the safety of
the valves, like bacteriological test and histology, are performed at the respective tissue bank as well as at corlife. Corlife
processes the tissues according to the approved process for DHV. The procurement organization is kept informed at all stages
of the process. After release the DHV is shipped either back to the procurement organization or directly to a clinic. Figure 2
shows a schematic illustration of the decellularisation process.
The original goal was to provide a total of 200 DHV. The center in Paris, originally part of the ESPOIR consortium, ceased, but a
center in Vienna, Austria, and one in Osaka, Japan, both outside of the consortium, joined. The goal of 200 DHV could not be
fully achieved, due to the time consuming approval procedures and restricted availability of homografts. Throughout the
project corlife received 158 pulmonary homografts for decellularization, 26 of them were not released for transplantation due
to donor specifics or bacterial contamination. 11 homografts were not implanted by end of 2016 as processing was not
completed until then.
Transport to the participating hospital was crucial as operation dates were already planned. All processed homografts were
transported safely and on time to the clinics. The safety concept of the decellularization process and the shelf life of the
decellularized valves have been further improved and corlife is working on a simplified procedure to enhance procurement.

WP4 Clinical Trial and Regulatory Affairs
Work package objectives

- Coordination of regulatory affairs for the formal approval of DHV by the authorities.
- Realization of the study according to the high standards of Good Clinical Practice (GCP) in all participating clinical centres including data monitoring.
- Selection and instruction of the patients.
- Operation of 200 patients within 36 months. Implantation of 25 DHV at each clinical side.
- To evaluate decellularized DHV for pulmonary heart valve replacement and to assess the growth potential of DHV and long term durability in comparison to current valve substitutes. In addition monitoring of postoperative clinical controls.
- Analysis of the data from the Clinical Trial for primary and secondary endpoints to enable Dissemination and Exploitation of the project results.
- Set up of a long term database to provide information about the durability of decellularized homografts.

Main results

A Study Protocol was designed by Hannover Medical School (MHH, partner 1) with the assistance of corlife (partner 9) and circulated to all partners. Case report forms and informed consent forms were implemented. The Clinical Trial Director Dr. Sarikouch (MHH) and representatives of corlife (partner 9), DGFG (partner 10) and EHB (partner 11) visited the different clinical centres for pre-trial organization. Together with the study centers, ethics votes were collected at each participating center and the supply with homografts and subsequently processed DHV were coordinated with national authorities.

Although all Member States apply the same European directives, national transposition is very heterogeneous. The time of the initiation of the clinical trial varied at the different centers and started at the last center not sooner than during the 4th year of the project ESPOIR. Without the backwind provided by the EC grant the implementation of the clinical trial and the cross border trafficking of homografts and DHV would not have been successful.

The study received the “ENCePP Study Seal”, which is granted by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) for following the ENCePP principles of standards, transparency and independence. The study was carried out properly, complying with all applicable national and international regulations. There were no deviations during implementation and during the study lifetime. A case report form was completed for each patient included. Monitoring visits at the different centers were performed by corlife throughout the whole duration of the clinical trial.

Serious Adverse Reaction (SAR) means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity (according to Directive 2004/23/EC). During the period, a total of 22 SAR were observed, 9 of them related to the DHV implantation. In 7 of the related cases, a suspected, clinical inapparent, bacterial infection of the recipient led to a SAR report, in two other cases, it was a stenosis shortly after surgery.

All SAR have been reported to the competent authorities, and, if applicable, to the respective procurement organization. Unfortunately there were two deaths within the ESPOIR clinical trial, which however, were unrelated to the study valve as they occurred due to myocardial failure after multi-valve procedures in two patients with severe congenital heart defects in Padua, Italy, and Zurich, Switzerland.

A total of 121 patients were implanted with DPH within the ESPOIR clinical trial. Figure 3 gives an overview of the patients operated at the different centres until 2017.

Follow-up monitoring of the patients was done directly after implantation, after 3, 6 and 12 months. Even after the end of the ESPOIR project all partners consented to provide annual follow up of all patients to acquire long-term data.
To this end, the ESPOIR Registry, a long-term database, was established. This Registry collects clinical data of all patients having received a non-cryopreserved decellularised homograft for pulmonary valve replacement since the first clinical implantation in 2002 in Chisinau, Moldavia. The ESPOIR Registry to date comprises data of 240 patients and shows an extraordinary result for freedom from explantation of 99 %.

An interim analysis has been done with the data of 234 patients, as by the time of this analysis 6 patients were not fully documented in the data base yet due to their recent surgery.

The perioperative and long term mortality is very low with 1.7 % in view of the large number of previous procedures in the patients operated and well within the expected mortality for pulmonary valve replacement according recent literature reports (Figure 4).

While 400 patients years were observed without an endocarditis in DHV 2 cases of proven bacterial endocarditis were observed within the last 6 months (Figure 5). This again is well within the expected range according recent literature reports, who report an annual 1% risk for endocarditis in patients with heart valve prostheses. The current risk for DPH endocarditis is 0.5 %.

DHV for PVR showed superior freedom from any re-intervention or re-operation after 10 years which is 83% for DHV in contrast to conventional cryopreserved homografts (60%) and bovine jugular vein conduits (Contegra®) 42% (Figure 6).

As a first conclusion of the ESPOIR clinical trial it can be said, that decellularized pulmonary homografts have shown safety and good early results. The size of the prospective cohort is unique and needs to be followed carefully. The goal is a 10-year follow up of all patients within the prospective trial and within the Registry. For further comparison studies all partners were asked to look for local matched cohorts for alternative treatment regimes. Publication of the ESPOIR 1-year data in comparison to bovine jugular vein conduits and standard cryopreserved homografts is planned for 2017.

WP5 Dissemination and Exploitation

Work package objectives

- To enable full transparency of the project activities of ESPOIR including regulatory and ethical issues.
- To enhance public awareness and understanding about the importance of tissue donation.
- To create two-way communication channels with patient groups, physicians/surgeons to exchange information and experience.
- To facilitate a targeted dissemination of ESPOIR objectives, approaches and results.
- To maximize the exploitation and impact of ESPOIR in clinical application.

Main results

Throughout the whole project the ESPOIR consortium disseminated information regarding the project itself, the decellularisation technology and the topic of tissue donation on an international level. Different types of audiences were targeted through various tools and diverse channels.

Seven target audiences were identified and continually addressed throughout the runtime of ESPOIR. The key message for all audience types was: “A new heart valve replacement, which is not rejected and potentially lasts a life time.” On a case by case basis the message was adapted slightly, as for example for political stakeholders the fact of lower costs due to less re-operations would be a important information.

In the following section the identified target groups with their relevance for the project and examples of ways they were addressed are listed.

General public:
Relevance of the target group: The ESPOIR study was supported by European taxes. Therefore, it was the projects’ responsibility to raise the awareness of the general public and inform them about this new medical technology and the outcome of the study.

Addressed via: The general public was targeted by the ESPOIR website, the project leaflets, press releases and interviews. Several presentations and events were organised especially made for the general public, like for example an event at Hannover Medical School (MHH, partner 1) around the topic of tissue donation for students of a professional medical school. In Germany two TV shows broadcasted sections about the ESPOIR study and the decellularisation technique. All information was given in basic language to make the aim and results of the project easy to understand for the civil society.

Patients:

Relevance of the target group: Patients were especially addressed to inform them about this alternative operation procedure and its advantages compared to the standard procedures. They should have the possibility to discuss different operation procedures with their surgeon and identify the most appropriate.

Addressed via: Patients were informed about the study within face-to-face meetings with their surgeons at the different participating clinical sites. However, the goal was to spread the information to a wide range of patients. Patients were reached by the same means as the general public. MHH organised a special seminar for patients during the 3rd Hannover Heart Congress in Germany. Moreover, patients were also addressed by establishing links to self-help groups and networks (please see below).

Self-help groups/networks:

Relevance of the target group: This target group was addressed as well to inform the patients. But moreover, self-help groups and networks serve as a multiplier for information transfer. Using the network channels one single information can be spread to several patients needing heart valve transplantation.

Addressed via: The ESPOIR website was linked to patient self-help groups within the European Congenital Heart Disease Organization and independent European information platforms like CORIENCE. The partners UNIPD and AOP (partners 5 and 7) established especially close connections to the Italian patient organisation “Un cuore un mondo - Padova” and supplied them with information on the study, e.g. by an explanatory video.

Scientific community:

Relevance of the target group: This target audience was divided into 2 different groups: surgeons and tissue banks / procurement organisations. To proactively inform the surgeons was one of the essential factors of dissemination and communication within the ESPOIR project. The decellularisation procedure and its advantages had to be understood and accepted by the surgeons first in order to guarantee the flow of information to the patients. The proactive information of tissue banks / procurement organisations was of very high relevance in order to guarantee a sufficient supply of homografts during and after the conduct of the ESPOIR study.

Addressed via: The interest of surgeons was raised by participation to the most relevant conferences in the area of cardiovascular surgery, such as the annual European EACTS conference. In addition, the clinical results of the first ten years of decellularized human heart valves for pulmonary heart valve replacement were published within the Journal of the EACTS in 2016. For the Techno College of the EACTS 2015 a 3D video showing the operation of the first ARISE patient was produced and used during several dissemination activities to spread information about decellularized heart valves. Special events were organised for surgeons and medical professional, like a workshop during the 4th Hannover Heart Congress in Germany. Corlife presented its technology at different fairs targeted to medical professionals. Furthermore information on the study and the decellularisation technique was published in 9 peer reviewed articles.

Tissue banks were sensitized to the decellularisation technology using two ways. First, the participating tissue banks presented the technology at several scientific thematic conferences, such as the annual EATB meetings, and second, the local
tissue banks of the participating clinics and outside of ESPOIR were contacted individually. As a result, dissemination and exploitation of the technology was performed in several face-to-face meetings.

Media:

Relevance of the target group: Different channels of the media can help spreading the key message and the results of the study to the general public and patients.
Addressed via: The media was regularly informed by press releases in the different participating countries and interviews were given to newspapers.

Political stakeholders:

Relevance of the target group: Political stakeholders were addressed to raise the awareness of the difficulties associated with the implementation of the Tissue & Cells Directives in the different European countries. Direct consultations with the competent authorities during valve approval and regular inspections were used to inform about the need for a uniform European Tissue Law respected by national legislation.
Addressed via: The exploitation manager, Dr. Harder, from corlife raised the interest of this target group by his active participation in the working parties “NA 027-02-21-01 AK Arbeitskreis Technische Mittel für das Tissue Engineering/ Tools for Tissue Engineering” of the German DIN Institute for Standardization and “CEN/TC 316: Medical products utilizing cells, tissues and/or their derivatives” of the European Committee for Standardization. Furthermore the project was presented to the Minister of Social Affairs and Health, State of Niedersachsen, Germany and to the EC representatives of the DG SANCO.

Further clinical sites and their local tissue banks:

Relevance of the target group: This target group was of very high importance in order to set up a network outside of the ESPOIR study. This network could be used to establish decellularized homograft transplantations at different clinical sides and guarantee the conduct of the procedure after the end of the ESPOIR study.
Addressed via: corlife established and will further establish strategic partnerships with further clinics (outside the ESPOIR consortium) and their local tissue banks. This target group was addressed individually in face-to-face meetings.

Additionally the consortium established several general tools for dissemination of the project ESPOIR:

Website:

The ESPOIR website was maintained and regularly updated with the latest information, e.g. with the latest numbers of the implanted valves at the different clinical centres. The website also offered a password protected section for the consortium to share information with each other.

Leaflet:

An ESPOIR promotional leaflet was designed, giving overview information about the project, the technology and the consortium. Corlife has also created a leaflet about its decellularized heart valves with basic information and explanatory schematics. The leaflets were distributed at different occasion.

Promotional video:

A promotional video dedicated to the general public was created together with the ARISE project. The video has initially been produced in German, but translated to English with sections of subtitles. It is called “Decellularized Heart Valves” (in German:
“Revolution aus dem Labor”) and runs 3:50 minutes. The video shows an interview with a young woman having received a decellularized aortic heart valve about 2 years ago. After the surgery she became pregnant. The risk of a pregnancy before the surgery would have been too high, as she had to take blood thinners. Moreover, short and simple information on the decellularization process and the operation procedure is given. The video was placed on different websites.

Wikipedia:

To address the civil society an article about “decellularized homografts” was published on Wikipedia with a link to the ESPOIR and ARISE websites. The article can be found via: https://en.wikipedia.org/wiki/Decellularized_homografts. Initially, the article has been published in English and German. Until today, it has been translated and published in Spanish, Italian, French and Russian as well. It is planned to further translate the article into Dutch and if possible to further languages.

Overall the ESPOIR consortium performed a total number of 178 dissemination activities and published 10 peer reviewed publications.

For a profitable exploitation of the decellularization technology corlife (partner 9) engaged in targeted meetings with clinics and procurement organisations. The technology has already been disseminated outside the ESPOIR consortium and the dissemination activities will continue: All hospitals of the consortium would like to continue with implantations of decellularized heart valves. The Medizinische Hochschule Hannover and the Children´s Hospital in Zürich are already doing so. Corlife is working on the conditions to export heart valves to Italy, which were not procured in Italy to ensure a supply of Padua. The other hospitals (Great Ormond Street London, Leiden, Leuven) still need to resolve the reimbursement. Beyond the consortium corlife has established cooperation in Austria, France, Germany (other than MHH), Japan, Spain, Switzerland and UK. The “Allgemeines Krankenhaus”, Vienna, Austria, has already performed 13 implantations. This clinic was keen to share their data with the ESPOIR consortium without receiving financial contribution by the EC.

Another 20 German hospitals successfully applied for reimbursement of decellularized homografts in 2017, stating an increasing interest in the technology.

Potential Impact:

Immediate impact of the Project ESPOIR

The ESPOIR project has been pivotal in many aspects. Approval of a decellularized human heart valve has not been applied for before in Europe. Accordingly, the competent authorities needed time to build up the necessary expertise for the authorisation of this type of new technology. ESPOIR PV is the first non-cryopreserved, decellularised human heart valve which has been approved in Europe for heart valve replacement. This authorisation led to significant interest of major (U.S.) companies in in the company Corlife.

Management of trans-border movement of human tissue preparations and the approval of a study testing a tissue preparation were also for the first time subject to authorization procedures in all participating countries. As there is no uniform legislation on the cross-border transport of human tissue preparations across Europe, the ESPOIR project has prepared the ground for new tissue engineering techniques in this regard. The project has helped tissue banks and authorities in specifying quality transfer agreements and shipping procedures for tissue preparations within Europe and to Japan.

The ESPOIR project has also been key in the field of congenital heart surgery as no prospective, multi-centre clinical trial had ever previously been performed in Europe to evaluate the use of homografts for pulmonary valve replacement. Local and national ethics committees were provided with appropriate information on the technique of decellularisation and its potential benefits for patients. The inclusion of children in such a study was deemed essential by ethics committees as the potential growth benefit would be only be evident after implantation in growing children. All ethics committees positively evaluated the ESPOIR study and issued approvals for clinical work. The study setting, which was also granted the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) study seal for transparency, can serve as a role model
for future clinical studies in the field of regenerative medicine.

The immediate regulatory impact of the ESPOIR project is evident in the approval process of a decellularised human heart valve for aortic valve replacement (ARISE AV), for ESPOIR’s “sister” project, ARISE which took less than one year. The initiation and start of a prospective clinical study evaluating ARISE AV for aortic valve replacement was undertaken in a timeframe that was two years faster that the corresponding approval process for the ESPOIR project. This highlights the pathfinding role of the ESPOIR project and the experience gained on the side of both applicant and authorities within the project, which will facilitate further clinical studies of tissue engineered products.

The ESPOIR project has made a significant contribution to the treatment of patients with congenital heart disease. As progress has been made in achieving survival for the majority of patients even in complex congenital heart diseases, the number of patients requiring pulmonary valve replacement is increasing steadily. Decellularised homografts have shown decreased reoperation rates in matched comparison to other currently available options for pulmonary valve replacement. However, the duration of follow-up and the number of patients treated before start of the ESPOIR project was limited.

Within ESPOIR it was possible to include 121 patients in the controlled prospective clinical trial at 7 clinical centres within Europe, which will provide follow-up data for the long-term evaluation of decellularized homografts in pulmonary valve replacement. Our multi-centre approach avoids bias arising from surgical centre effects, i.e. particular surgical techniques deployed at individual centres. Multi-centre studies are at the current time quite uncommon in congenital heart surgery and may be the best option for evaluation of a new product in terms of safety in daily clinical practice.

The ESPOIR Registry was also established within the project lifetime. This Registry collects the clinical data of all patients who have received a non-cryopreserved decellularised homograft for pulmonary valve replacement since the first clinical implantation in 2002 in Chisinau, Moldavia. These first clinical implantations used pre-seeding with stem cells. Since 2005 only non-seeded decellularized homografts have been used. The ESPOIR Registry currently comprises data of 240 patients and shows an extraordinary result for freedom from explantation of 99 %. This Registry will allow a robust assessment of decellularised heart valves for pulmonary valve replacement, including but not limited to diameter development and regenerative capability. It is a unique resource as, so far, no comparable prospective long term data on the effects of tissue processing of donated human heart valves are available at any homograft bank.

Ethical issues, which are particularly important in the evolving field of regenerative medicine, have been directly addressed within ESPOIR via the Ethics and Governance Council. Clear and transparent information on these aspects has been made available via the project website to minimize patient concerns and to raise awareness among the general public throughout Europe regarding the importance of tissue donation, in line with the aims of the EU Tissue Directive (2004/23/EC).

Beyond these wider-reaching impacts, ESPOIR also contributed to significant impacts at the level of the involved partners, their organisations and surroundings:

MHH:

The ESPOIR project enabled deeper collaboration with experienced European centers for the treatment of congenital heart disease and facilitated closer collaboration with partners outside the ESPOIR project. A number of potential future projects have been discussed as well as training exchange programs for young surgeons. Potential future projects may focus, for example, on the evaluation of decellularised monocuspid valves in the repair of tetralogy of Fallot, the most common congenital heart malformation with cyanosis. International collaboration outside the field of congenital heart disease was also promoted, e.g. in the field of ventricular assist systems for patients with heart failure.

The ESPOIR project was a key element in the international peer-reviewed re-evaluation of the Excellence Cluster REBIRTH
“From Regenerative Biology to Reconstructive Therapy” as it exemplarily demonstrates the translation from basic research to routine clinical use. Junior researchers within the TECAS ITN European Doctoral Academy in Regenerative Engineering, a Marie Curie Training Network, also benefitted from the experience made within the ESPOIR project as a living example of European-wide cardiovascular research.

The experience gained within the ESPOIR project enabled a second proposal on decellularised homografts, this time focusing on the challenging aortic position, which was successfully submitted under the HORIZON 2020 research and innovation program and was selected for funding under grant agreement No. 643597.

SMPHU:

The ESPOIR project revolutionizes the surgical approach to heart valve disease by establishing a novel regenerative approach to therapy. The SMPHU clinical centre has provided state-of-the-art operative treatment for all 12 patients within the clinical trial of DHV for pulmonary valve replacement and thus had the opportunity to be at the forefront of clinical research in this exciting new field of cardiovascular tissue engineering, strengthening European excellence and leadership in this field.

LUMC:

LUMC acknowledges the value of decellularized homografts for surgical replacement of the pulmonary valve in both children and adults with congenital heart disease and has intensified the use of homografts in this population. In addition, the importance of the technique was decisive in LUMC’s decision to participate in the ARISE project, with the aim of reintroducing the use of homografts for aortic valve replacement in the clinic. LUMC will continue to study the efficacy of decellularized homografts.

GOSH:

The decellularization process has raised great interest within the Great Ormond Street Hospital for Children NHS Trust. This particular study has supported three post-doctoral researchers of the clinic, all of them being visiting researchers from other European countries. The international collaboration has also raised the awareness of the process in the home countries of the visiting researchers. Additionally the clinic is planning a new research project on the topic in cooperation with other clinics from EU countries and further discussions are about to take place in the near future.

UNIPD & AOP:

UNIPD and AOP have appreciated the clinical results of the Project and are making joint efforts to ensure the continuity of the program as an extension to the common clinical practice for patients affected with congenital or acquired heart valve disease. The centers are lobbying the regional health care system to reimburse the costs resulting from the decellularization process.

Basic research on decellularized pulmonary homografts (DPH) has been initiated in parallel with the clinical trial. The centers have developed a novel surgical model of DPH implantation in a rodent model in order to deepen their knowledge and to try to solve several unanswered questions and controversies regarding tissue-guided regeneration, such as autologous cell repopulation time points, stem cell turnover, and macrophage activation. A paper on this work has been submitted to an international medical journal. A thesis of a medical graduate from the University of Padova has been completed describing this research (title of the thesis: “Decellularized pulmonary homografts implantation in GFP-positive animal models: new decellularization protocol evaluation and experimental evidence of autologous cell repopulation capacity.”). One chapter of this thesis describes the clinical impact of the ESPOIR Project in the centre.

Continuing contacts have been implemented with the association “Un Cuore Un Mondo – Padova Onlus”, a voluntary based
association of parents of children with congenital heart diseases that aims supporting families involved in the same experience. Among other activities, the association has widely distributed the project leaflets through its network and has produced and disseminated a video informing the patient community of the DPH advantages and its use. The dissemination activities have attracted the attention of the local and national media and at least 10 articles have been published in different newspapers during the lifetime of the project. As a result, the patients UNIPD and AOP have treated with DPH implantation come not only from Veneto Region, but from other two neighboring regions as well.

UZH:

The University of Zurich is the umbrella organization under which the University Children’s Hospital and the University Hospital function. Both these hospitals are centres of excellence with repute throughout Switzerland and beyond. In the departments of cardiac surgery the most complex cases of congenital heart disease in children and adults are treated. UZH is the first and only clinic in Switzerland participating in the ESPOIR Trial. They are a reference Centre for the treatment of valvar heart diseases in childhood, adolescence and in young adults. With the availability of the ESPOIR valve, they now have a new treatment option for these patients. The study has triggered UZH to further continue and involve in research programs for tissue engineering and regenerative medicine. The team of UZH has been disseminating the progress of the project during their interactions with other clinicians and new collaborations with other clinical entities have been established. By virtue of this trial, UZH has gotten sensitized about tissue and valve donation. Together with EHB, they have started a program to further optimize their donation program and make it more efficient. They will follow their patients, who received an ESPOIR valve, during short, middle and long term and the collected data will be published in the near future.

Corlife:

The project has contributed significantly to the development of corlife as a company and acceptance of the decellularization technology. The EC support has created an umbrella under which the partners jointly looked for solutions for procurement, cross-border shipment of human tissues, clinical application and cooperation between charitable organizations and corlife. Not all problems could be solved within the project. In particular, the cooperation with some procurement organizations remains problematic, as cooperation with a company is basically rejected, even if all statutory requirements are fulfilled. Since these organizations control the tissue donation, this can lead to limited access to cell-free heart valves in selected regions.

During the runtime of the project, the application of DHV has been incorporated into the “Operation & Procedure Code”. The code covers all medical interventions in Germany and similar codes exist in the Member States and Switzerland. This is an important step towards transparency in the use of DHV and for statistical reporting.

The project has led to an increase in strategic partnerships. Outside the consortium, partnerships with procurement organizations in Austria, Germany, Italy, Japan and the Netherlands have been established. Cooperation with an US organization is currently being negotiated. Furthermore, corlife is also cooperating with clinics outside of the consortium: Osaka (Japan) and Vienna (Austria).

An important prerequisite for the reimbursement of the high costs for the DHV by the health insurance funds is a positive benefit assessment. Publications on the DHV have been and continue to be very important as scientific evidence. The arguments published to date have provisionally convinced health insurance companies in Austria, Germany and Switzerland. Further study results will help the DHV to be recognized as an affordable therapy.

A total of 22 German clinics have already successfully applied for reimbursement in 2017. Based on this number, corlife expects an additional demand of at least 100 heart valves for decellularization. Already during the term, new, qualified employees were recruited. With the expansion of the product range and the increased demand, corlife plans to hire more staff.
Encouraged by the positive feedback and the excellent results from the project, corlife is planning further products and improvements. In addition to the decellularized pulmonary and aortic valves, further decellularized tissues are in line to be approved as products. The procedures for procurement are further simplified to allow more clinics to participate.

Corlife has established a cloud-based information platform (“iTissue”) in which all documents related to processed tissues are filed. Collaborative tissue banks have access to “their” data. The competent authorities have access to all data at any time. Corlife thus creates the greatest possible transparency in the handling of donated tissues. The system will facilitate the search for the ideal implant and enable the exchange of information between procurement organizations, corlife and physicians.

DGFG:

Within the 5-year lifetime of ESPOIR, DGFG has worked and connected across Europe for the dissemination of the promising technology of decellularizing human heart valves prior to implantation as a replacement of a malfunctioning pulmonary valve.

After approval of ESPOIR PV the clinical trial started in the setting of a so-called non-interventional trial, which means that the heart valve is implanted according current guidelines and according its authorisation following surgical indication for a decellularised heart valve. About 50 percent of 121 patients were supplied with DGFG homografts (pulmonary valves). Within the project period a minor disadvantage was posed by specific regulations and national laws, especially within countries beyond the EBH/DGFG network, which led to problems for EU-wide procurement and EU-wide allocation.

The procurement from post mortem donors takes place in a specific environment. Clinical rooms were audited at DGFG and the training of staff took place. Cardiovascular tissue from post-mortem donors was taken for microbiological testing. Unfortunately, this task could not be fully completed, but the subject is further pursued within the ARISE project. Nevertheless, through the intention to expand the donation of domino heart valves – in particular from young donors - the cooperation with further individual clinical network partners was intensified and further cooperation with heart centres in Germany was established.

EHB:

As a tissue establishment with very high flow of donation and implantation of cardo-vascular tissue grafts, the European Homograft Bank is convinced that decellularization is a method that will have significant impact regarding the cardio-vascular tissues designated for clinical application: no occurrence of immune related problems, no need for multiple surgical procedures in the youngest categories of cardiac patients and a solution for issues related to the growth of small patients. These facts will convince the paediatric cardiac surgical community that the use of these grafts will revolutionize future treatment for small (and young) patients.

Regarding future developments, EHB suggests that increasing numbers of pulmonary valves, needed for reconstruction of the right ventricular outflow tract (RVOT), should be decellularized and used for the repair of congenital malformations as soon as possible after birth to avoid the significant cardiac complications due to the impaired function of their malformed native valves. One-stage final repair might be the solution for the majority of those patients.

The European Homograft Bank is committed to continue working in both directions: in one hand continuing to cryopreserve the cardiac valves for the group of patients showing excellent results with those grafts (e.g. young adult patients with congenital pathology of the valves) and, on the other hand, supporting decellularization as the perfect solution for the newborns, children and other patients showing accelerated deterioration of the conventional allografts.

In order to have the sufficient number of available grafts for both categories, EHB has been working and will continue to work
on the sensitization of the community for more post-mortem donations, in particular in some EU Member States which still have low rates of organ and tissue donation. This can only be made possible through the communication with the broader audiences, using the media and other methods to inform the general public, participating at meetings of general practitioners and nurses, teaching at training courses of the transplant coordinators, organizing debates regarding the donation after death, etc.

Regarding this point, the most important route for the future for the EHB is to increase donations from the non-heart beating deceased donors. This donor category might increase the number of available heart valves and vascular allograft considerably. To achieve this, the multiple actors involved in the management of the persons dying suddenly or those dying soon after a brain injury (emergency services, ICU, etc.) need to be more involved in the donation process and be more emotionally attuned to this very human activity.

KU Leuven:

By participating in the ESPOIR clinical trial, the treating doctors (cardiologists and cardiac surgeons) are more familiar with the DHV process for the pulmonary valve. These participating doctors were able to convince local doctors of the promising results of the DHV pulmonary valve and this led to a common use of the DHV valve in the centre of KU Leuven by the end of the project. The intermediate follow-up results confirm the hypothesized advantages concerning structural valve deterioration. The knowledge about decellularization and the early clinical results have convinced referring physicians of its potential as well.

The clinic has acknowledged the importance of the decellularized valve and the need for it to enter regular clinical practice in Belgium. Hopefully, this can be achieved in the near future.

The project has also led to good cooperation between different EU centres and results will continue to be shared and discussed after the end of the project as well, which will lead to a better treatment for the patients included in the study and future patients. This collaboration may also lead to further insights for the use of the DHV pulmonary valve.

Potential long-term impact of the Project ESPOIR

The potential for sustainable, long-term impacts is already evident in the field of regulation of new products emerging from tissue engineering techniques. At the time of Corlife’s application for the approval of the decellularized pulmonary heart valve in 2012, it was unclear to which regulatory body the application should be submitted, indicating the complex hurdles faced by the project. Despite its purely mechanical function as a heart valve, the regulatory decision taken for ESPOIR has meant that any human tissue preparation will be treated as a medicinal product in Germany, the Netherlands, Belgium, U.K. Italy and Moldavia. In Switzerland, the decision was taken that decellularized human heart valves will be considered as medical devices. These clarifications will allow for much faster regulation of similar products in the future to the benefit of innovative companies coming to the market offering services and products based on human tissue designing and processing.

The long-term impact of ESPOIR in view of a potential conflict of interests between tissue banks working on a not-for-profit basis and a company providing processing as a commercial service cannot be fully estimated at present. However, it was clarified within the ESPOIR project that such service may not negatively impact current procedures where, where the procuring tissue banks are fully responsible for allocation based on a uniform price for every patient in need of such a graft.

Experiences from ESPOIR will also help tissue banks to implement new processing steps within the procurement of human heart valves and other tissue as they became familiar with the quality standards and requirements for decellularised grafts issued by the authorities. In the future, tissue banks may even provide sophisticated tissue designing services themselves.

The decellularisation of human heart valves - or humanized animal valves - as a technique holds the potential to change the
status quo for the clinical application of cardio-vascular tissue. If the early results based current data can be confirmed in the long-term, then the reduced immunogenic response in patients will lead to a corresponding reduction in re-operation rates and consequently will mean a decrease in mortality rates and improvements in the quality of life for patients with congenital heart defects.

The extent of spontaneous recellularisation, i.e. the population of the decellularised valve with the patient’s own cells, will determine the real long-term fate of the transplanted heart valve. In addition, a normal cell-type composition is necessary as basis for autologous regeneration of the transplanted collagen matrix. Conducting planned biopsies in patients for the purposes of follow-up is not an option for ethical reasons and conclusions can be therefore only be derived in the rare cases of necessary procedures or unplanned operations. The ESPOIR project members are currently preparing a publication summarizing their current work on spontaneous recellularisation of decellularized human heart valves in vivo.

The potential for lifelong durability of the valves tested within the ESPOIR project represents a fundamental break with other currently available options for heart valve replacement: planned re-operations are regularly required for biological valve prostheses and mechanical prostheses significantly reduce the quality of life of the recipients. With the ESPOIR heart valves, primary heart valve replacement during the initial repair of congenital heart defects may become feasible. If the long-term results are positive, current algorithms for heart valve replacement may have to be revisited. At present, valve replacement is delayed as long as possible to avoid more frequent re-operations. The lifelong durability of the valves would allow valve replacement to be carried out at an earlier time point than currently recommended, e.g. in the context of chronic pulmonary regurgitation. Improvements in the decellularisation technology also can be expected for the future, e.g. through the application of growth factors facilitating recellularisation by recipient’s own cells.

While the availability of donated human heart valves is main limitation of our current technique, a major breakthrough can be expected once humanized valves of animal origin are available for decellularisation. In future scenarios such as these, Corlife oHG will benefit from the experience garnered within the ESPOIR project in terms of communication with competent authorities for approval, large scale processing and quality assurance measures. Clinical implantation of such humanized tissue-engineered heart valves, e.g. originating from α–Gal knock-out animals, will need prior testing in clinical studies, which can also draw the ESPOIR model for clinical studies in regenerative medicine.

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Result In Brief

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