E·S·P·O·I·R

Surveillance Protocol 2013-11, 06.11.2013

European Clinical Study for the Application of Regenerative Heart Valves – ESPOIR

Prof. Dr. Axel Haverich, MHH, Principle Investigator — 06/11/2013

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PASS information	
Title	European Clinical Study for the Application of Regenerative Heart Valves – ESPOIR (the "Surveillance")
Protocol version identifier	Surveillance Protocol 2013-11, 06.11.2013
Date of last version of protocol	October 2013
Register numbers	ENCePP Study Ref. Number 5064 clinicaltrials.gov: NCT 02 035 540
Active substance	Human pulmonary valve
Medicinal product	decellularized human pulmonary valve, Espoir PV ("ESPOIR PV")
Product reference	PEI.G.11634.01.1
Procedure number	OPS (Germany): 5-351.37, 5-352.28, 5-354.29, 5-358.25, 5-359.0
Marketing authorisation holder(s)	corlife oHG ("corlife") Feodor-Lynen-Straße 23 D-30625 Hannover, Germany
Joint PASS	No

Research question and objectives	The purpose of this investigation is to evaluate decellularized human pulmonary valve, Espoir PV ("ESPOIR PV") for pulmonary valve replacement rates in comparison to current valve substitutes within a large prospective multicentre surveillance at 8 leading European Centres for Congenital Cardiothoracic Surgery regarding re-operation and re-intervention, hemodynamic performance, growth potential and long term durability. Primary safety endpoints: Rate of cardiovascular adverse reactions, leading to e.g. re-operation, catheter based interventions. Secondary safety data: Collection of medical data to assess the process of tissue vigilance. Collection of medical history to support the presence/absence of adverse events, e.g. infections, arrhythmia. Primary efficacy endpoint: Freedom from valve dysfunction leading to re-intervention or explanation at end of the Surveillance. Key secondary efficacy endpoint: Diameters of ESPOIR PV at end of the Surveillance in comparison to diameters at implantation, transvalvular gradients, valve competence assessed by non-invasive imaging tools such as echocardiography or cardiac magnetic resonance imaging.
Countries of study	Germany, Republic of Moldova, The Netherlands, United Kingdom, Italy, France, Switzerland, Belgium
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1. Table of Contents

2. List of abbreviations

AHA	American Heart Association
AR	Adverse Reaction
BE	Belgium
CH	Switzerland
CRF	Case Report Form
CRP	C-reactive protein
CVD	Cardiovascular diseases
CW Doppler	Continuous-Wave Doppler
DE	Germany
DHV	Decellularized heart valve
EC	Ethics Committee
ECHDO	European Congenital Heart Disease Organisation
EGC	Ethics and Governance Council
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESPOIR PV	Decellularized human pulmonary vale, Espoir PV
EU	European Union
FR	France
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
Hb	hemoglobin
IT	Italy
IRB	Institutional Review Board
LDH	Lactatdehydrogenase
LOCF	„last observation carried forward“
MD	Republic of Moldova
MRI	Magnetic Resonance Imaging
NL	The Netherlands
NYHA	New York Heart Association
PEI	Paul-Ehrlich Institute
PVR	Pulmonary valve replacement
PW Doppler	Pulsed-Wave-Doppler
STS Guidelines	Guidelines for reporting morbidity and mortality after cardiac

	valvular operations. Ad hoc liaison committee for standardizing definitions of prosthetic heart valve morbidity of the American association for thoracic surgery and the society of thoracic surgeons.
UK	United Kingdom
SAR	Serious Adverse Reaction
SDC	Sodium Desoxy Cholate
SDS	Sodium Dodecyl Sulphate
SME	Small and Medium-sized Enterprises
TOF	Tetralogy of Fallot

3. Responsible Parties

3.1 Market Authorisation Holder / Sponsor

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3.4 Local Investigators

All Local Investigators are reported in the Investigators contact list (Annex 1), as amended.

The coordinating Local Investigators are:

Clinical Centre	Department	Local Investigator
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Universitatea de Stat de Medicina si Farmacie „Nicolae Testemitanu“, SMPHU, Republic of Moldova	Cardiac Surgery Centre	Prof. Dr. Anatol Ciubotaru

Clinical Centre	Department	Local Investigator
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c/o Centre for Ethics and Law in the Life Sciences,
Leibniz Universität Hannover
Im Moore 21, 30167 Hannover, Germany
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4. Abstract

Title	European clinical Study for the Application of regenerative heart valves – ESPOIR Protocol No. 2013-11, version date 06.11.2013 main author: PD Dr. med. Samir Sarikouch, Medizinische Hochschule Hannover
Rationale and background	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 paediatric patients. ESPOIR PV hosts the power to regenerate.
Research question and objectives	Evaluation of decellularized human heart valves for pulmonary heart valve replacement in comparison to current valve substitutes. Safety endpoints include cardiovascular adverse events, time to re-operation, re-intervention and explantation. Efficacy endpoints include freedom from valve dysfunction and hemodynamic performance.
Study design	This is a prospective, non-randomized, single-arm, multi-centre surveillance study to be conducted in Europe. The Surveillance is designed as a study, where ◦ ESPOIR PV is prescribed in the usual manner in accordance with the terms of the approval. ◦ The assignment of the patient to a particular therapeutic strategy is not decided in advance by this Surveillance Protocol but falls within current practice and the prescription of ESPOIR PV is clearly separated from the decision to include the patient in the Surveillance.

	◦ No additional diagnostic or monitoring procedures shall be applied to the patients ◦ and epidemiological methods shall be used for the analysis of collected data.
Population	Inclusion criteria: Indication for pulmonary valve replacement according to current medical guidelines. Signed Informed consent of legal guardians or patients, assent of patients. Exclusion criteria: The patient shall not suffer from generalized connective tissue disorders (eg, Marfan syndrome), or active rheumatic disorders or severe asymmetric calcification of the valve ring. The coronary arteries of the patient shall not be in abnormal position or heavily calcified. Patients shall not show hypersensitivity against Sodium Dodecyl Sulphate, Sodium Desoxycholate, human collagen (or other elastic fibers) or Benzonase®. The patient has not provided Surveillance informed consent. Duration of Participation: After valve implantation, patients will be followed and assessed at discharge, 3-, 6-, 12- and, if applicable,24- months thereafter.
Variables	Primary safety endpoints: Cardiovascular Adverse Reactions; Serious Adverse Reactions, such as infections, immunological reactions, etc. Secondary safety endpoints: Blood Parameters as additional safety data to support presence/absence of Adverse Reactions; Time to reoperation, explantation and/or death. Primary efficacy endpoint: Freedom from valve dysfunction leading to re-intervention or explantation at end of the study. Secondary efficacy endpoint: Diameters of ESPOIR PV at end of the study in comparison to diameters at implantation, transvalvular gradients, valve competence assessed by noninvasive imaging tools such as echocardiography or cardiac magnetic resonance imaging

Data sources	All medical data will be collected on specific case report forms (CRF). These data and or related personal data will be collected within the sole responsibility and the reasonable discretion of each Surveillance Centre. Personal data shall only be collected in a scope that is necessary for the treatment of the patient. No additional personal or health data shall be collected in connection with the Surveillance. Data and safety monitoring will be performed by an independent Ethics and Governance Council (EGC).	
Study size	This Surveillance will enrol a minimum of 200 patients implanted with ESPOIR PV.	
Data analysis	Actuarial analysis according to Kaplan-Meier will be used to show estimated probability of freedom from each AR. Actuarial analysis takes into account both early and late post-operative events. The time from ESPOIR PV implantation to endpoint ESPOIR PV dysfunction that requires either a catheter-based or a surgical procedure will also be calculated according Kaplan and Meier.	
Milestones	Start of data collection:	December 2013
	End of data collection:	December 2016
	Registration in the EU PAS register:	November 2013
	Final report of study results:	December 2017

5. Amendments and updates

This Protocol replaces Version 2013-10

The reason is the adjustment to the “Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies”, issued 26.09.2012, EMA/623947/2012.

6. Milestones

Milestone	Planned date
Registration in the EU PAS register	November 2013
Start of data collection	December 2013
Progress report	January 2015
Progress report	January 2016
End of data collection	December 2016
Final report of study results	December 2017

7. Rationale and background

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 [1]. 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 [2] with the resulting total financial burden estimated about 169 billion Euro per year [1, 3].

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 paediatric patients.

Haverich et al. 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, 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 [4].

Starting in 2002, Haverich et al. were one of the first research teams to report clinical application of tissue engineered heart valves in paediatric patients. Initially DHV was applied in combination with seeding of autologous progenitor cells [5,6,7,8] and growth of the DHV was demonstrated [6]. Active seeding became unnecessary as spontaneous re-endothelialization of DHV by circulating endothelial progenitor cells was observed.[4] Since then non-seeded, decellularized heart valves have been used throughout.

The DHV was approved on 22/08/2013 by the German competent authority as the tissue preparation "ESPOIR PV" (PEI.G.11634.01.1) for pulmonary valve replacement. In any other state (BE, CH, FR, IT, MD, NL, UK) further approvals are or will be obtained (Annex 1).

Meanwhile, more than 80 children and young adults have been treated with DHV for pulmonary valve replacement in Chişinău/MD and Hannover/DE and the results have been presented at the Annual Scientific Meeting of the American Heart Association (AHA) in November 2010, published in September 2011 as well as during the ESPOIR Kick-off meeting in 1/2012 [9,10,11]. Although these represent early clinical results only, none of these valves has needed to be explanted due to degeneration or rejection, and immunological follow-up has so far revealed no abnormalities in these patients. Moreover, a near physiological development of valve diameters was observed.

As with any patient undergoing heart valve replacement, patients in this Surveillance may experience AR which may include, but are not limited to, the following: angina, haemorrhage, arrhythmia, cardiac arrest, endocarditis, heart failure, haemolysis, myocardial infarction, prosthesis pannus, (non)-structural valve dysfunction, perivalvular leak, stenosis, stroke, regurgitation, re-operation or explantation, thromboembolism, valve thrombosis and/or death. All cardiovascular AR will be evaluated in relationship to the valve using the revised STS guidelines [12].

No procedures in this Surveillance are experimental. Participating in this Surveillance is thought not to induce any additional risk to patient undergoing pulmonary valve replacement.

8. Research question and objectives

The purpose of this investigation is to ESPOIR PV for pulmonary valve replacement rates in comparison to current valve substitutes within a large prospective multicentre surveillance at 8 leading European Centres for Congenital Cardiothoracic Surgery regarding re-operation and re-intervention, hemodynamic performance, growth potential and long term durability.

This will be a non-randomized surveillance involving a minimum of 200 isolated pulmonary valve replacement patients receiving ESPOIR PV processed by corlife.

The following outcome variables will be analyzed:

8.1 Safety endpoints, Vigilance

8.1.1 Primary safety endpoints

Rate of cardiovascular AR, e.g. re-operation, catheter based interventions.

8.1.2 Secondary safety data

Collection of medical data to assess the process of tissue vigilance. Collection of medical history to support the presence/absence of AR, e.g. infections, arrhythmia.

8.2 Efficacy endpoints

8.2.1 Primary efficacy endpoint

Freedom from valve dysfunction leading to re-intervention or explanation at end of the Surveillance.

8.2.2 Key secondary efficacy endpoint

Diameters of ESPOIR PV at end of the Surveillance in comparison to diameters at implantation, transvalvular gradients, valve competence assessed by non-invasive imaging tools such as echocardiography or cardiac magnetic resonance imaging.

9. Research methods

9.1 Study design

This Surveillance is designed as a prospective, non-randomized, study (as there is no experimental procedure) involving a minimum of 200 patients receiving ESPOIR PV for pulmonary valve replacement according current medical guidelines in congenital heart disease. A single-arm clinical Surveillance design was chosen since extensive data on conventional alternatives is available in the literature.

Long term follow-up of all patients beyond the Surveillance is recommended for complete evaluation of ESPOIR PV with respect to current life expectancy of patients and the potential of ESPOIR PV for lifelong durability.

9.2 Setting

9.2.1 The Consortium

The European clinical study for the application of regenerative heart valves is an EU-Commission funded project driven by a consortium of eight university hospitals (Sec. 3.4), the company corlife (Sec. 3.1) and Deutsche Gesellschaft für Gewebetransplantation, Hannover, Germany, and European Homograft Bank, Brussels, Belgium ("Project Partner"). Object of Espoir is the conduct of Surveillance.

All Project Partners are parties to the Consortium Agreement concluded under the Seventh Framework Program pursuant to Regulation No 1906/2006 of the European Parliament and the Council of 18 December 2006 relating to the project "European Clinical Study For The Application Of Regenerative Heart Valves (the "Consortium Agreement") and are parties to the Grant Agreement concluded pursuant to the "Rules For Participation And The European Grant Agreement" adopted on 10 April 2007 (the "Grant Agreement"), which provide for the framework of the cooperation in the EU-funded project Espoir and which regulate the Parties' reimbursement of costs in the project Espoir.

9.2.2 Surveillance

The Surveillance is designed as a study, where

- ESPOIR PV is prescribed in the usual manner in accordance with the terms of the approval.
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by this Surveillance Protocol but falls within current practice and the prescription of ESPOIR PV is clearly separated from the decision to include the patient in the Surveillance.
- No additional diagnostic or monitoring procedures shall be applied to the patients
- and epidemiological methods shall be used for the analysis of collected data.

The decision to prescribe ESPOIR PV is made as part of normal patient care and is independent of this Surveillance Protocol or the decision to include a patient in this Surveillance. The participant is only subjected to examinations and investigations that are considered to be part of the normal clinical care.

9.2.3 Centre selection

European centres specializing in the surgical treatment of Congenital Heart Defects will cooperate in the ESPOIR Surveillance to enable recruitment of a sufficiently sized study population for robust statistical and reliable clinical evaluation of ESPOIR PV in comparison to conventional heart valve substitutes. An European-wide network of 8 clinical centres has thus been established to take adequate account of the heterogeneity of patients and to eliminate any bias in patient selection or bias resulting from a particular surgical technique, influence of the surgeon or treatment algorithms. Centres were chosen for their excellent results in congenital heart defect repair and their high-volume surgical programs. The size of the Surveillance cohort (n=200) was calculated to reliably compare ESPOIR PV to established pediatric heart valve substitutes.

9.2.4 Patient Enrolment and Surveillance Timeline

The proposed recruitment of 25 patients from each of these clinical centres within 24 months is realistic given the number of pulmonary valve replacements (PVR) in these institutions every year. Furthermore, it is anticipated that patient demand will increase, as there already is a large waiting list at Hannover Medical School for

potential ESPOIR PV recipients. The calculated cohort size of 200 patients will allow for a thorough evaluation of re-intervention rates, hemodynamical performance and durability of ESPOIR PV for PVR in congenital heart disease. Patient recruitment is expected to be completed within 24 months after start of the Surveillance. Data analysis will be performed 36 months after start of the Surveillance to ensure a minimal follow up of 12 months for all Surveillance patients.

9.2.5 Donor Selection for ESPOIR PV

All tissue donors comply with the requirements of the Directives 2004/23/EC and 2006/17/EC. The same criteria apply that are applied to the donation of homografts.

9.2.6 Valve Description

Scaffolds for tissue engineered heart valves can also be derived by decellularization of valve grafts of human or animal origin by chemical treatment. The remaining connective tissue forms the matrix for the new valve as it is recellularized by recipient cells. Decellularized fresh valve grafts of the same species are well accepted by the recipient, as demonstrated in animal models [4,13]. However, cryopreserved decellularized homografts, have failed in pediatric patients [14,15,16]. According to Narine et al. cryological conservation seems to be detrimental for decellularized grafts, since structural properties of the scaffold tissue are significantly affected by cryopreservation.[17] Xenogenic matrices have been the basis for commercially available tissue engineered pulmonary valve substitutes and have been implanted surgically in a considerable number of patients. However, these have shown conflicting results suggesting adverse immunological reactions [18]. Based on extensive long-term large animal experiments and recent auspicious early clinical results, the ESPOIR project puts forward a novel regenerative solution for the shortcomings of currently available valve substitutes in the form of a valve substitute with the ability to regenerate by autologous recellularization, integrate completely into the recipient heart and thus facilitate growth and sustained valve integrity.

To date, Hannover Medical School (MHH) has implanted more than 80 fresh, non-cryopreserved, non-seeded, decellularized only homografts (DHV), for pulmonary valve replacement, in children and young adults. MHH has demonstrated reduced reoperation rates in age and heart defect matched children with glutaraldehyde-fixed

Contegra® xenografts and conventional cryopreserved homografts for a follow-up period up to 5 years.[9] Freedom from degeneration was significantly higher in DHV. These grafts did not develop significant gradients in contrast to Contegra® xenografts and cryopreserved homografts. None of the implanted DHV has had to be explanted so far which represents an outstanding result in comparison to conventional heart valve substitutes. Immunological follow-up of DHV patients has revealed no abnormalities to date.

DHV has further demonstrated a trend towards adaptive growth.[9] The exact growth potential of implanted DHV cannot yet be precisely determined so far as most initial implantations have been oversized for safety reasons. However, definitive growth assessment can be expected after implantation of DHV in neonates and infants, which was started this year in Hannover and will be verified within the Surveillance.

9.2.7 Legal Aspects

ESPOIR PV has been approved by the Paul-Ehrlich-Institute for marketing pursuant to Section 20c of the German Drug Law (Arzneimittelgesetz) by approval no. PEI.G.11634.01.1 dated 22.08.2013. Corlife qualifies as a so-called tissue establishment pursuant to administrative decision no. 41401/H-137 by the Staatliches Gewerbeaufsichtsamt Hannover, Germany.

The German authorities concluded, that ESPOIR PV are covered by the Directive 2004/23/EC (the "Tissues & Cells Directive"), since they are originally derived from human tissue: Article 2 (1) of the Tissues & Cells Directive provides that*" the […] Directive shall apply to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications."* As a result, the German authorities qualify the ESPOIR PV as a so-called "tissue preparation" pursuant to Section 21a of the German Drug Law (*Arzneimittelgesetz*) which must be prepared/produced in accordance with the German rules and regulations implementing the provisions of the Tissues & Cells Directive into German law.

The German authorities concluded further, that ESPOIR PV is not an ATMP according to Article 2 (1) (b) of the Regulation (EC) 1394/ 2007 on advanced therapy medicinal products (the "Advanced Therapies Regulation"): "*[p]roducts containing or*

consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition".

The German authorities further concluded that ESPOIR PV is not a medical device according to Article 1 (5) (e) of the Medical Devices Directive 93/42/EEC: "*[t]his Directive does not apply to […] transplants or tissues or cells of human origin nor to products incorporating or derived from tissues or cells of human origin, […]."*

ESPOIR PV is processed in accordance with the requirements of the Tissues & Cells Directive and the corresponding provisions of the German Drug Law as well as in compliance with other applicable German laws (such as the German Federal Data Protection Act) under involvement of accredited establishments.

The Sponsor is not aware of any European Directive or Regulation limiting the import and export of tissue preparations among Member States, once approval has been granted. Article 9 of the Tissues & Cells Directive only provides for specific proceedings for the import of tissues from third countries (i.e., non-EU Member States). Although, the Tissues & Cells Directive in connection with Directives 2006/17/EC and 2006/86/EC set forth specific requirements on the donation, procurement, testing, processing, conservation, storage and distribution of tissues and for the establishments and persons involved in the aforementioned activities, the Tissues & Cells Directive does not set forth specific approval requirements on specific tissues or tissue preparations.

However, since national laws of the EU Member States can be stricter than the requirements of the relevant EU-Directives, some countries impose specific, and/or additional requirements on the import of the ESPOIR PV.

In contrast to the EU-Member-States, the Swiss authorities concluded, that ESPOIR PV is a Medical Device and not a tissue preparation, as set forth above.

9.2.8 Valve Implantation Records

As the product has been approved by the competent authorities, the Local Investigator will maintain a log of all valves implanted for the evaluation at the centre. The log shall include:

1. patient Surveillance number

2. main diagnosis
3. valve number
4. valve size
5. date of implant

Corlife will also provide an Implant Identification Card for every patient.

9.2.9 Valve Storage

The storage environment should be clean, cool, and dry. Store ESPOIR PV at 2°C to 8°C (36°F to 46°F). The ESPOIR PV has been qualified for a maximum storage life of 60 days from the date of tissue donation. The expiry date of the device is recorded on the outer package label.

9.2.10 Patient Population

A majority of congenital heart defects affect the right ventricle and thereby the pulmonary valve [19]. One good example for this type of congenital malformations is Tetralogy of Fallot (TOF), the most common cyanotic heart defect. Surgical repair of Tetralogy of Fallot has been performed for more than 50 years[18, 20]. Current perioperative mortality is around 2% in experienced centres[21] and 30 years life expectancy today is more than 90% [22,23]. However, there is late mortality due to sequelae such as chronic pulmonary valve regurgitation, associated with progressive right ventricular dilatation, arrhythmia and sudden cardiac death [24,25,26,27]. In this context it is important to note that in many countries of the western world, the adult population with repaired TOF exceeds the pediatric population [28].

Timing of pulmonary valve replacement in the setting of common severe pulmonary regurgitation nowadays is usually based on “unisex” right ventricular volume “thresholds” in combination with clinical signs of heart failure and/ or arrhythmia [29,30,31,32]. Surgery is ideally performed before the right ventricle becomes irreversibly damaged as a result of longstanding volume and/or pressure overload [33].

The routine practice of cardiovascular surgery employed by the Local Investigator will determine the indications for replacement of a patient's natural pulmonary valve or previously implanted prosthesis. Due to the complexity and variations in surgical procedures for congenital heart disease, and the individual anatomy and other patient

related factors, the choice of surgical technique and approach is left to the discretion of the individual surgeon.

The decision to treat the patient with ESPOIR PV is independent from participation in this Surveillance.

9.2.11 Inclusion Criteria

The following inclusion criteria will be used in this Surveillance:

1. Indication for pulmonary valve replacement according to current medical guidelines in heart disease
2. Informed consent of legal guardians or patients, assent of patients

9.2.12 Exclusion Criteria

1. The patient has not provided Surveillance informed consent.
2. The patient shall not suffer from
   a. generalized connective tissue dis-orders (eg, Marfan syndrome), or
   b. active rheumatic disorders, or
   c. severe asymmetric calcification of the valve ring.
3. The coronary arteries of the patient shall not be in abnormal position or heavily calcified.
4. Patients shall not show hypersensitivity against sodium dodecyl sul-phate (SDS), sodium desoxycholate (SDC), human collagen (or other elastic fibers) or Benzonase®.

9.2.13 Surveillance Procedures

Corlife will provide the Surveillance-sites with the Surveillance Protocol and Case Report Forms (CRFs), and, on request, with all other related documentation. Corlife will conduct all aspects of data quality assurance (data review and, if needed, monitoring of Surveillance sites, to eliminate ambiguities). Each Surveillance site should adhere to all the requirements specified in this protocol and the CRFs. Assessments of patients should be obtained by the Local Investigator for the preoperative, operative, and

discharge period and postoperatively at 3, 6 and 12 months and 24 months, as applicable. An assessment beyond the Surveillance will be subject of a separate Surveillance/agreement.

The Local Investigator should make every attempt to follow the patients and should document the information gathered during the follow-up visits on the CRFs. The patients should be encouraged by the Local Investigator to report any address or telephone number changes to the Local Investigator. They should also be informed of the importance of returning for scheduled follow-up visits even if they are not having any problems. If a patient is lost to follow-up the efforts undertaken to locate the patient should be documented.

All patient's personal and health data shall be collected within the sole reasonable discretion of the Local Investigator and only in a type and scope required for the specific medical treatment of a patient. No additional personal or health data shall be collected by the investigators and this Surveillance does not require the collection or use of any personal or health data in addition to such data that is required for the specific medical treatment of a patient.

9.2.14 Preoperative Procedures

The Local Investigator should screen all isolated pulmonary valve replacement cases for participation in the Surveillance.

The indication for pulmonary valve replacement with ESPOIR PV will be solely based upon the current clinical guidelines in the Local Investigators institution.

The Local Investigator should determine and document whether each patient meets the selection criteria previously outlined before enrolment into the Surveillance. The Local Investigator will also obtain informed consent for Surveillance participation from each patient or parents, and informed assent from children, prior to implantation of an ESPOIR PV. A patient identification number (Sec. 9.4) shall be assigned to each patient who signs a consent form. If a patient is enrolled in the Surveillance, however the Surveillance valve is not implanted, an explanation should be indicated on the patient selection form of the CRF. No further Case Report Forms should be completed for these patients.

The Local Investigator should determine and record each patient's demographics (date of birth, sex), height, weight, New York Heart Association (NYHA) functional

class, cardiac rhythm, past and present cardiovascular and non-cardiovascular conditions and previous cardiovascular operations. An echo shall be performed. The investigator should seek to provide preoperative information on right ventricular function based on magnetic resonance imaging (MRI) imaging in all cases and provide copies to the MRI Core Laboratory in Hannover; however, MRI is not mandatory in children needing anaesthesia for the MRI scan. Copies of the MRI should be provided to:

corlife oHG
ESPOIR / CRF
Feodor-Lynen-Straße 23
D-30625 Hannover

Corlife will pass on these copies to the MRI Core Laboratory in Hannover.

9.2.15 Operative Procedures

The surgical technique employed will be that developed and perfected by the Local Investigator in his/her normal practice of cardiac surgery. Special attention should be given to proper sizing, orientation and irrigation of the valve during surgery.

The Local Investigator should record the implant date, implanting surgeon, etiology, diagnosis for current replacement, information regarding the particular valve implanted (including size, number, suture technique) and other details concerning the surgery such as condition of the annulus/valve being replaced, debridement procedures, concomitant procedures and intra-operative AR.

9.2.16 Discharge

At discharge, the Local Investigator should record the date of the patient's discharge from the hospital, patient status, cardiac rhythm and AR. Echo/Doppler evaluation is required at discharge. The requested clinical and echocardiographic variables at discharge are outlined in Annex 1.

9.2.17 Postoperative Follow-up Visits (3, 6, 12 months, and 24 months, as applicable)

The postoperative follow-up will be that developed and perfected by the Local Investigator in his/her normal practice. The following is recommended:

Postoperative follow-up visits are recommended at 3 months, 6 months, one year, and, if applicable, two years. If studies are performed at other times in response to symptoms, the Local Investigator should document these studies as an interim visit.

Doppler/echocardiography are recommended for all patients at all visits. Cardiac magnetic resonance imaging is routinely performed in all patients within one year after the implantation of the Surveillance valve. However MRI is not mandatory in children needing anaesthesia for the MRI scan. Copies of the MRI scans shall be provided to the MRI Core Laboratory in Hannover (Sec. 9.2.13).

It is recommended, that at each postoperative assessment, the Local Investigator should determine the patient's availability for future follow-up. If any patient needs to be seen at other than a regularly scheduled follow-up visit, obtained information should be documented by the Local Investigator on the follow-up Case Report Form and indicated as an interim visit.

9.2.18 Patient Withdrawal

The Local Investigator should make reasonable attempt to follow the patient at each of the required assessment periods. Patients may withdraw from the Surveillance without penalty or loss of benefits to which they are otherwise entitled. A Surveillance patient that has been withdrawn from the Surveillance will not be replaced.

If a participant, who has given informed consent, withdraws or loses capacity to consent during the Surveillance, the participant would be withdrawn from the Surveillance. Identifiable data already collected with consent would be retained and used in the Surveillance.

9.2.19 Missed Visit / Lost to Follow-Up

If a patient cannot be reached for a follow-up visit, the Local Investigator should document on the respective CRF the effort(s) he/she made to contact that patient or the patient’s primary health care provider. If the patient cannot be reached in any way the assessment will be considered as missed visit for that time interval. At subsequent scheduled follow-up visits, new efforts should be undertaken to locate the patients.

9.3 Variables

9.3.1 Outcome Variables (Safety and Efficacy)

Four outcome variables based on CRF information will be analyzed by the Sponsor together with the Study Director and the Study Statistician:

1. Primary safety endpoints:
    a. Cardiovascular AR
    b. SAR, such as infections, immunological reactions, etc.
2. Secondary safety endpoints:
    a. Blood Parameters as additional safety data to support presence/absence of AR
    b. Time to reoperation, explantation and/or death
3. Primary efficacy endpoint: Freedom from valve dysfunction leading to re-intervention or explantation at end of the study.
4. Secondary efficacy endpoint: Diameters of ESPOIR PV at end of the study in comparison to diameters at implantation, transvalvular gradients, valve competence assessed by noninvasive imaging tools such as echocardiography or cardiac magnetic resonance imaging.

9.3.2 Primary Safety Endpoint: Cardiovascular AR

The "Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations" (STS guidelines) were approved by the Council of the Society of Thoracic Surgery (STS), published in September 1988 and revised in 1996. This Surveillance of cardiovascular AR should be conducted in accordance with the revised STS guidelines. In reporting AR, all cardiovascular related symptoms, including abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, congestive heart failure, cardiac failure, and myocardial infarction should be assessed as to their relation to the valve.

The Local Investigator should record all new AR (i.e. not previously reported adverse reactions). All pertinent details related to the AR and evaluation of the valve relatedness should be completed in accordance with the revised STS guidelines. If an

adverse reaction results in reoperation/valve explantation or death, the Local Investigator will complete the respective CRF. Copies of an autopsy report and/or death summary should be included with the CRF's. The Local Investigator should make reasonable effort to return the explanted valve(s) (at autopsy or reoperation) to corlife. Return kits for explanted valves will be provided upon request by corlife.

The primary safety objective is to assess the rate of all cardiovascular AR /complication rates for ESPOIR PV and the process of tissue vigilance.

9.3.3 Secondary Safety Data

The following data should be collected: Hb, LDH, Haptoglobin, CRP, Leukocytes. Blood studies should be performed within 7 days preoperatively and at discharge. Blood data will support the absence/presence of related AR. For example, hemolysis should be reported as an adverse event if anemia is present; however, in the absence of anemia, hemolysis will be considered to be compensated and does not require reporting. Time to events, such as death, reoperation including explantation will be evaluated for those outcomes, calculated from the date of operation.

9.3.4 Primary Efficacy Endpoint: Freedom from valve dysfunction

Echocardiographic studies should be obtained and analyzed at discharge and at 3, 6 Months and at annual follow-ups. The requested variables include peak and mean systolic gradient, using pw and cw doppler, in the right ventricular outflow tract. The echo evaluation (videotape or CD) should remain at the Surveillance site, but be available to corlife Surveillance personnel upon request. The MRIs will be analyzed by the MRI Core Laboratory at Medical School in Hannover (Sec. 9.2.13) for potential valvular stenosis, via phase contrast flow measurements in the main pulmonary artery and for valvular competence, via phase contrast flow measurements and by ventricular volumetry. MRI cine images will be used to visualize the Surveillance valve in patients with poor echocardiographic windows.

9.3.5 Secondary Efficacy Endpoint: ESPOIR PV diameters and right ventricular function

Diameters of ESPOIR PV at end of the Surveillance will be analyzed in comparison to diameters at implantation and to age matched reference values. Preoperative

noninvasive data on right ventricular size and function, such as right ventricular end diastolic, end systolic volume, ejection fraction and ventricular mass will be derived from MRI and compared to postoperative status.

9.4 Data sources

9.4.1 Management of Personal Data

All medical data will be collected on specific case report forms (CRF) provided by Sponsor. Any medical data and or related personal data will be collected within the sole responsibility and the reasonable discretion of each Surveillance Centre. Personal data shall only be collected in a scope that is necessary for the treatment of the patient. No additional personal or health data shall be collected in connection with the Surveillance.

Each patient/participant in the Surveillance shall provide his or her consent to the collection and use of his/her personal data by the health personnel of the treating Surveillance Centre. No personal health data must be disclosed to Sponsor, the Principle Investigator, the Study Director or any other person participating in the Surveillance without the prior written consent of the patient.

Medical data shall only be reported to Sponsor on the CRFs provided by Sponsor in anonymized fashion. For ensuring appropriate anonymization, each Surveillance Centre shall assign a three-digit patient number for each patient participating in the Surveillance. Such patient number shall be randomly created by each Surveillance Centre by using a combination of capital letters and numbers. None of the letters and numbers used when creating a patient number must be related to the specific patient (e.g., the use of name initials or numbers from a patient's birth date are not permitted). It is important that each patient number is randomly created without application of any system or coding mechanism. Each CRF shall only contain such patient number and no other data that would allow the Sponsor or any other person participating in the Surveillance to identify a reported patient. Each Surveillance Centre is prohibited from disclosing personal data of a patient/participant in the Surveillance to the Sponsor or any other person participating in the Surveillance. In order to avoid any potential detriments to a patient for the lack of disclosure of his or her personal data to the Sponsor, investigator, or any other person participating in the Surveillance, each Surveillance Centre is obligated to immediately direct any notifications made to a Surveillance Centre under a patient number to the specific patient such notification

relates to.

9.4.2 Data and Safety Monitoring by the Ethics and Governance Council

Data and safety monitoring is a requirement for conducting a Surveillance in a clinical context and is usually undertaken by a body consisting of a statistician, an expert in ethics and a medical expert. Data and safety monitoring will be performed by the independent Ethics and Governance Council (EGC), which for this purpose was extended by an expert statistician in the field of congenital heart disease, Prof. Siegfried Kropf, Magdeburg. The EGC includes 2 experts in ethics, Prof. Nils Hoppe, Hannover and Dr. Karen Melham, Oxford as well as Prof. Sir Magdi Yacoub, London as one of the leading cardiothoracic surgeons in the world and Marte Jystad, Oslo of the European patient organization ECHDO. The EGC convenes regularly with the Surveillance Director and the Principle Investigator.

The members of the EGC serve in an individual capacity and provide their expertise and recommendations. The responsibilities of the EGC are to 1) periodically review and evaluate the accumulated Surveillance data for participant safety, Surveillance conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to the Sponsor concerning the continuation, modification, or termination of the study. The EGC considers Surveillance-specific data as well as relevant background knowledge about the disease, test agent, or patient population under Surveillance. For this purpose, the EGC will only have access to anonymized medical data as recorded on CRFs (Sec. 9.4.1, 9.6.1).

Corlife shall report any SAR pursuant to Section 11 and any statistical analysis pursuant to Section 9.7 to the EGC and, if required, to the competent authorities and the tissue banks providing the homografts. The EGC is responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

9.5 Study size

The size of the Surveillance cohort (n=200) was chosen to reliably

1. proof the process of tissue vigilance;
2. compare ESPOIR PV to established paediatric valved conduit prostheses.

This would suffice to show, with 80% power, a difference in freedom from endpoint between 90% (ESPOIR PV) and 77% (comparison group) at 3 years with 5% error probability. The actually expected event free percentages may vary slightly according to the resulting definitive patient cohort (ESPOIR PV) composition.

The comparison group would either derive from the literature or a matched pair comparison group. Contemporary patient cohorts operated with Contegra®-conduits and cryopreserved homografts are established at the Surveillance sites.

9.6 Data management

9.6.1 Case Report Forms (CRFs)

Paper-based Case Report Forms (CRFs) for individual patients will be provided by corlife. All CRFs must contain a specific three-digit patient number created in each Surveillance Centre. The centres shall assign a three-digit patient number for each patient participating in the Surveillance. Such patient number shall be randomly created by each Surveillance Centre by using a combination of capital letters and numbers. None of the letters and numbers used when creating a patient number must be related to the specific patient (e.g., the use of name initials or numbers from a patient's birth date are not permitted). It is important that each patient number is randomly created without application of any system or coding mechanism.

Personal patient data shall not be contained on any CRF. The Local Investigator or its designee (Surveillance Centre) should keep a separate log of patient names and current addresses to facilitate record keeping and the ability to contact patients for future follow-up. The separate log of patient names, or any personal data contained in the log, shall not be made available to the Sponsor or other participants in the Surveillance. Completed CRFs shall be forwarded exclusively to Sponsor. Neither Sponsor nor Local Investigator or Principal Investigator or Study Director or Medical Statistician shall disclose completed CRFs to the other participants in the Surveillance.

CRFs shall support the Local Investigator when collecting data. CRFs shall not influence the physician in collecting data beyond the established policy at the respective site. The Local Investigator shall only collect data that is relevant for the individual patient's medical treatment with an ESPOIR PV. The Sponsor does not provide the Local Investigator with instructions for data collection.

CRFs are collected by the Sponsor for scientific analysis only. Sponsor will not intervene or discuss with the Local Investigator (Surveillance Centre) details on the investigator's medical treatment of individual patients on the basis of information contained in a CRF or otherwise.

CRFs will be used as an integral part of the Surveillance and subsequent reports. Therefore, the forms should be legible and complete. Not missing data (for whatsoever reason) should be lined out. Errors should be lined out, but not obliterated and the correction inserted, signed and dated by the investigator. Copies of changed CRFs must be provided to the Sponsor and retained in the patient Surveillance file.

A CRF should be completed and signed by the Local Investigator or designee listed in the Clinical Studies Agreement for each subject receiving a Surveillance valve, including subjects withdrawn from the Surveillance for any reasoning a timely manner. The reason for withdrawal should be noted on the CRF by the Local Investigator for each subject. Since there is a potential for errors, inaccuracies, and illegibility in transcribing data onto CRF's, originals or photocopies of all relevant operative records and reports, postoperative examinations, laboratory and other test results should be kept on file.

CRF's and copies of test results should be available to the Sponsor for evaluation. CRF's should be kept current to reflect subject status at each phase during the course of the Surveillance. Completed CRF's should be sent to the address below in a timely manner after the patient's discharge or follow-up:

corlife oHG
ESPOIR / CRF
Feodor-Lynen-Straße 23
D-30625 Hannover

9.6.2 Statistical software

The software SPSS, Vers. 21 (or higher), will be used.

9.7 Data analysis

Sections 9.7.1, 9.7.2 detail the analysis approach for each of the Surveillance outcomes. Sections 9.7.3, 9.7.4 address the issues of data poolability and missing data. Unless otherwise noted, all statistical tests will be performed at the $\alpha = 0.05$ level.

9.7.1 Primary Safety Endpoint

For reporting purposes, all cardiovascular AR within the early post-operative period (within 30 days of implant) will be summarized by the percent of patients who experience an AR. Linearized rates will be used to summarize AR for the late (>30 days) post-operative period. The linearized rates will be reported as the number of events occurring after the early post-operative period per year of patient exposure. Actuarial analysis according to Kaplan-Meier will be used to show estimated probability of freedom from each AR. Actuarial analysis takes into account both early and late post-operative events.

9.7.2 Secondary Safety Endpoints

Blood data (Hb, LDH, Haptoglobin, CRP, Leukocytes) will be collected preoperatively and at discharge. This blood data will support the absence/presence of related AR; in particular hemolysis and leucocytosis. Data will be reported as the percent of patients with results within the normal ranges at each time interval. The percent of patients with hemolysis at each point will also be reported. Summaries will be presented for the entire Surveillance cohort and will also be stratified by valve size.

Time to death from the date of operation will be analyzed by the method of Kaplan and Meier. Time to reoperation from the date of operation as well as time to explant from the date of reoperation will be similarly analyzed. For time to explantation and time to reoperation, the time to first explantation or reoperation will be calculated for those patients requiring explantation or reoperation. These analyses will also be reported stratified by valve size. Analyses for time to explantation and time to reoperation will also be stratified by fatal versus non-fatal reactions.

9.7.3 Efficacy Analysis: Freedom from valve dysfunction

The time from ESPOIR PV implantation to endpoint ESPOIR PV dysfunction that requires either a catheter-based or a surgical procedure will be calculated according Kaplan and Meier. Matched comparison to conventional cryopreserved homografts and bovine jugular vein grafts will be performed to compensate for known effects of patients age, number of previous operations and complexity of the congenital heart defect.

9.7.4 Efficacy Analysis: ESPOIR PV diameters and right ventricular function

For secondary endpoints it is also planned to undertake matched comparisons to conventional cryopreserved homografts and bovine jugular vein grafts. In addition, appropriate growth of ESPOIR PV will be assessed in comparison to age matched reference groups using valve diameter z-scores and/or standard deviation scores.

9.7.5 Poolability

Patient baseline risk will be statistically compared between all participating centres. Statistics will be provided by the Surveillance Statistician (Sec. 3.5). Chi-square tests will be used to compare categorical risk factors while analysis of variance will be used to compare continuous risk factors. Comparisons will be based on the following demographic and pre-operative variables: age, sex, underlying congenital heart defect, previous (heart valve replacement) surgery, valvular lesion, pre-operative NYHA, concomitant cardiac procedures, and coexisting cardiovascular conditions. Also included in the analysis will be the size of implanted valve. Additional analyses, such as propensity score matching, may be performed if the need arises.

9.7.6 Missing Data

All statistical tests on the efficacy endpoints will be performed two ways: (1) using only those patients with no missing data at baseline and one year (complete case) and (2) by the method of last observation carried forward (LOCF). The complete case and LOCF analyses will be compared. However, the method of last observation carried forward will be used in addition to the complete case analyses (i.e. analyses based on only those patients with baseline and one year data) for the comparison of NYHA classification and hemodynamic performance to baseline at one year to investigate the effect of loss-to-follow-up. NYHA classification and hemodynamic performance will still be summarized at each of the time points described in the previous version of the protocol. However, these data will only be statistically compared to baseline at one year.

9.8 Quality control

9.8.1 Local Investigator Responsibilities

The Local Investigator is responsible for obtaining IRB/EC approval for the Surveillance at his/her Institution and by competent authorities, as applicable. The study will not start before this approval has been sent to corlife and to the Study Director.

Surveillance records including CRF's, signed Local Investigator's Agreement, originals of all blood and hemodynamic studies, signed informed consents, IRB/EC approval letters, documentation of IRB/EC submissions, and other documents pertaining to the conduct of the Surveillance should be kept on file by the Local Investigator.

The responsibilities of the Local Investigator(s) comply with the requirements set forth in Declaration of Helsinki, the local laws of the country – including regulations of the European Union and the regulations given by Good Clinical Practice (GCP) and Good Vigilance Practice (GVP). The Local Investigator(s) should adhere to the regulations that provide the greatest protection to the patient. Any protocol deviations should be fully documented and explained on the CRF and reported to the local IRB/EC if applicable. Any unusual or unanticipated adverse reaction should be reported immediately to the Sponsor (Sec. 11) and if applicable, to the IRB/EC as outlined in the Local Investigator's Statement and Agreement. If deemed necessary by the Principal Investigator, the IRB/EC, or the Sponsor, the investigation may be suspended pending a thorough Surveillance of the incident.

If the Local Investigator wishes to assign the files to someone else or move them to another location, he should inform the Sponsor and the concerned patients in writing. If there is a change or addition of Local Investigators, an amended Local Investigator's Agreement should be completed promptly. Any other personnel changes should be reported immediately to the Study Director to schedule a training program. Evaluation visits will be scheduled throughout the course of the Surveillance. It is essential that the Local Investigator set aside a sufficient amount of time for these visits to permit an adequate review of the Surveillance's progress, completed CRFs and original records.

9.8.2 Sponsor / Surveillance Monitor Responsibilities

A Surveillance monitor assigned to the Surveillance by the Sponsor may monitor the progress of the Surveillance. The Surveillance monitor must be acquainted with the Local Investigator and other key people involved in the Surveillance. The Surveillance monitor will remain in close contact with the site throughout the duration of the Surveillance to answer any questions concerning CRFs. The Surveillance monitor will be responsible for reviewing CRFs on their legibility and suitability for scientific analysis, will inquire with the Local Investigator on potentially missing data, and will be visiting the site periodically to monitor Surveillance progress and compliance with the Surveillance protocol. The local data protection laws will be followed. The Surveillance monitor shall not have access to the original patient file but shall only have access to anonymized patient data. Monitoring visits will be scheduled throughout the duration of the Surveillance at a mutually convenient time for the monitor and principal investigator or designee. Monitoring will be conducted along Good Clinical Practice (GCP), as applicable.

Contact data of Surveillance monitors:

Ms Nicolin Heister: nicolin.heister@corlife.eu
Ms Dr. Carmen Puschmann: carmen.puschmann@corlife.eu
Tel. +49 511 563539 57, Fax: +49 511 563539 55

9.8.3 Data and safety monitoring by the independent Ethics and Governance Council (EGC)

Data and safety monitoring will be performed by the independent Ethics and Governance Council (EGC), which includes an expert statistician in the field of congenital heart disease, 2 experts in ethics, a cardiothoracic surgeon and a member of the European patient organization ECHDO.

The responsibilities of the EGC are to 1) periodically review and evaluate the accumulated Surveillance data for participant safety, Surveillance conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to the Sponsor concerning the continuation, modification, or termination of the study. The EGC considers Surveillance-specific data as well as relevant background knowledge about the disease, test agent, or patient population under Surveillance. For this purpose, the EGC will only have access to anonymized medical data as recorded on

CRFs.

9.8.4 Audits and Inspections

In the event that audits are initiated by competent authorities, the Local Investigator shall allow access to the original medical records to such and provide all requested information.

9.9 Limitations of the research methods

The results may be biased due to the open, non-randomized, non-controlled design. The analytical methods (physical examination, echocardiography) are known, established, harmonized by guidelines but not standardized. MRI data are analyzed by the Study Director to avoid subjective factor in the analysis.

However, the limitations can indeed affect but not distort the result. Primary safety endpoints are AR and reinterventions. These endpoints are clearly definable and are not subject to individual interpretation.

9.10 Other aspects

None.

10. Protection of human subjects

The Surveillance will, as far as applicable, adhere to the regulations that provide the greatest protection to the patient including the requirements set forth in the:

- Declaration of Helsinki;
- Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells; and
- Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and

testing of human tissues and cells; and

- Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, as amended;
- Laws of the respective country – including regulations of the European Union; and
- Grant Agreement 278453, Article 7, Special clause 15 (Sec. 9.2.1): "The beneficiary(ies) shall provide the Commission with a written confirmation that it has received (a) favourable opinion(s) of the relevant ethical committee(s) and, if applicable, the regulatory approval(s) of the competent national or local authority(ies) in the country in which the research is to be carried out before beginning any Commission approved research requiring such opinions or approvals. The copy of the official approval from the relevant national or local ethics committees must also be provided to the Commission."
- Grant Agreement 278453, Article 7, Special clause 16.1 (Sec. 9.2.1): "The beneficiary(ies) shall provide the Commission with a statement confirming that it has received (a) favourable opinion(s) of the relevant ethics committee(s) and, if applicable, the regulatory approval of the competent national authority(ies) in the country concerned before beginning any biomedical research involving human beings."

10.1 Informed Consent and Institutional Review Board (IRB) / Ethics Committee (EC)

For purposes of this Surveillance, and to comply with European Data Protection Laws, written informed consent will be obtained from all patients and/or legal guardians as well as informed assent by participating children. The patient must be adequately informed of his/her participation in the clinical Surveillance and what will be required of him/her in order to comply with the protocol. The patient will be informed that confidentiality and anonymity will be maintained at all times. In addition, informed

consent is required to allow appropriate data monitoring including access to medical records by the Sponsor and regulatory agencies. Minors who are capable of discernment, should also sign the informed consent form.

Non-binding examples for the information and informed consent form are given in Annex 1. The centres are encouraged to use the documents that are valid in the relevant country.

The IRB/EC should approve the informed consent and protocol for use at its institution prior to enrolment of the first patient. A written statement by the IRB/EC indicating approval of the informed consent and protocol must be submitted to the Sponsor prior to enrolment. These approvals will be forwarded to the European Commission as they are part of the Grant Agreement.

10.2 Insurance for Clinical Subjects

The product ESPOIR PV, used in this Surveillance, is covered by product liability insurance. Corlife will not provide insurance in addition to such coverage.

11. Management and reporting of adverse events/adverse reactions

11.1 Adverse Reaction (AR)

An AR is any untoward medical occurrence in a subject which does not necessarily have to have a causal relationship with Surveillance treatment. An AR can therefore be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease, temporary or permanent, whether or not related to the ESPOIR PV implantation. AR information will be collected throughout the Surveillance. AR (event, date of onset, severity, duration, and relationship to device) should be recorded (Adverse Reaction data) by the Local Investigator.

11.2 Serious Adverse Reaction (SAR)

'Serious Adverse Reaction' means an unintended response, including a communicable disease, in the recipient associated with the application of ESPOIR PV that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity (Article 3 (n), Directive 2004/23/EC).

SAR includes, but is not limited to:

1. death
2. serious deterioration in the health of the subject that
    a. resulted in a life-threatening illness or injury;
    b. resulted in permanent impairment of a body structure or a body function;
    c. required in patient hospitalization or prolongation of existing hospitalization;
    d. resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
    e. led to fetal distress, fetal death or congenital abnormality or birth defect.

11.3 Reporting AR

AR are reported in the CRF.

11.4 Reporting SAR

The Local Investigator(s) should report any SAR during the investigation to the Sponsor within 24 hours after the Local Investigator(s) first learns of the event. Notification should be done

1. to corlife via Fax. +49 511 563 539 55. SAR notifications to corlife should not include any personal patient data;
2. to the local tissue bank having imported ESPOIR PV, if applicable;
3. to the local competent authority;
4. to Ethics Committee EC/IRB in accordance with the EC/IRB requirements.

A template for SAR reporting is delivered with each and any ESPOIR PV. The Sponsor will forward all valve-related SAR to the EGC.

11.5 Autopsy/Death

The Local Investigator shall make reasonable efforts to obtain a copy of the autopsy report and/ or death summary. Information on the cause of death and its relationship to the Surveillance device should be determined by the Local Investigator and recorded as an SAR. Anonymized copies of an autopsy report, if available, and/or a death summary should be included with the CRF.

11.6 Explanted Valves

Patients who have the Surveillance valve explanted are exempt from further follow-up 30 days post-explant. Every effort should be made to return the explanted valve(s) (at autopsy or reoperation) to corlife. Return kits for explanted valves are provided upon request by corlife.

12. Plans for disseminating and communicating study results

Corlife will submit the required regulatory reports, such as SAR reports, withdrawal of IRB/E, approvals of the competent authorities, recall information , as applicable.

Corlife will report progress reports to the Local Investigators and the EGC.

The final report will be submitted to the Local Investigators, the EGC, the competent authorities, the EC/IRB, the ENCEPP and the European Commission.

The Consortium will publish all major results of this Surveillance within 12 months after discharge of the last patient.

Any and all publication of the principal results from any single center experience within the study needs prior written approval from the coordinator and the publication committee as outline in the Consortium Agreement.

13. References

[1] Health. Http://ec.Europa.Eu/health/major_chronic_diseases/diseases/cardiovascular/index_en.Htm. 2010

[2] Eurocat. 2010:http://www.eurocat-network.eu

[3] Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged european union. Eur Heart J. 2006;27:1610-1619

[4] Baraki H, Tudorache I, Braun M, Hoffler K, Gorler A, Lichtenberg A, Bara C, Calistru A, Brandes G, Hewicker-Trautwein M, Hilfiker A, Haverich A, Cebotari S. Orthotopic replacement of the aortic valve with decellularized allograft in a sheep model. Biomaterials. 2009;30:6240-6246

[5] Lichtenberg A, Cebotari S, Tudorache I, Hilfiker A, Haverich A. Biological scaffolds for heart valve tissue engineering. Methods Mol Med. 2007;140:309-317

[6] Cebotari S, Lichtenberg A, Tudorache I, Hilfiker A, Mertsching H, Leyh R, Breymann T, Kallenbach K, Maniuc L, Batrinac A, Repin O, Maliga O, Ciubotaru A, Haverich A. Clinical application of tissue engineered human heart valves using autologous progenitor cells. Circulation. 2006;114:I132-137

[7] Lichtenberg A, Tudorache I, Cebotari S, Ringes-Lichtenberg S, Sturz G, Hoeffler K, Hurscheler C, Brandes G, Hilfiker A, Haverich A. In vitro re-endothelialization of detergent decellularized heart valves under simulated physiological dynamic conditions. Biomaterials. 2006;27:4221-4229

[8] Lichtenberg A, Tudorache I, Cebotari S, Suprunov M, Tudorache G, Goerler H, Park JK, Hilfiker-Kleiner D, Ringes-Lichtenberg S, Karck M, Brandes G, Hilfiker A, Haverich A. Preclinical testing of tissue-engineered heart valves re-endothelialized under simulated physiological conditions. Circulation. 2006;114:I559-565

[9] Cebotari S, Tudorache I, Ciubotaru A, Boethig D, Sarikouch S, Goerler A, Lichtenberg A, Cheptanaru E, Barnaciuc S, Cazacu A, Maliga O, Repin O, Maniuc L, Breymann T, Haverich A. Use of fresh decellularized allografts for pulmonary valve replacement may

reduce the reoperation rate in children and young adults: Early report. Circulation. 2011;124:S115-123

[10] Neumann A, Sarikouch S, Breymann T, Cebotari S, Boethig D, Horke A, Beerbaum P, Westhoff-Bleck M, Harald B, Ono M, Tudorache I, Haverich A, Beutel G.
Early systemic cellular immune response in children and young adults receiving decellularized fresh allografts for pulmonary valve replacement.
Tissue Eng Part A. 2013 Oct 20. [Epub ahead of print]

[11] Neumann A, Cebotari S, Tudorache I, Haverich A, Sarikouch S. Heart valve engineering: decellularized allograft matrices in clinical practice. Biomed Tech (Berl). 2013 Oct 1;58(5):453-6.

[12] Edmunds LH, Jr., Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ad hoc liaison committee for standardizing definitions of prosthetic heart valve morbidity of the american association for thoracic surgery and the society of thoracic surgeons. J Thorac Cardiovasc Surg. 1996;112:708-711

[13] Zhou J, Fritze O, Schleicher M, Wendel HP, Schenke-Layland K, Harasztosi C, Hu S, Stock UA. Impact of heart valve decellularization on 3-d ultrastructure, immunogenicity and thrombogenicity. Biomaterials. 2010;31:2549-2554

[14] da Costa FD, Dohmen PM, Duarte D, von Glenn C, Lopes SV, Filho HH, da Costa MB, Konertz W. Immunological and echocardiographic evaluation of decellularized versus cryopreserved allografts during the ross operation. Eur J Cardiothorac Surg. 2005;27:572-578

[15] da Costa FD, Santos LR, Collatusso C, Matsuda CN, Lopes SA, Cauduro S, Roderjan JG, Ingham E. Thirteen years' experience with the ross operation. J Heart Valve Dis. 2009;18:84-94

[16] Simon P, Kasimir MT, Seebacher G, Weigel G, Ullrich R, Salzer-Muhar U, Rieder E, Wolner E. Early failure of the tissue engineered porcine heart valve synergraft in pediatric patients. Eur J Cardiothorac Surg. 2003;23:1002-1006; discussion 1006

[17] Narine K, Ing EC, Cornelissen M, Desomer F, Beele H, Vanlangenhove L, Smet SD, Nooten GV. Readily available porcine aortic valve matrices for use in tissue valve engineering. Is cryopreservation an option? Cryobiology. 2006;53:169-181

[18] Ruffer A, Purbojo A, Cicha I, Glockler M, Potapov S, Dittrich S, Cesnjevar RA. Early failure of xenogenous de-cellularised pulmonary valve conduits--a word of caution! Eur J Cardiothorac Surg. 2010;38:78-85

[19] Lindinger A, Schwedler G, Hense HW. Prevalence of congenital heart defects in newborns in germany: Results of the first registration year of the pan Surveillance (july 2006 to june 2007). Klin Padiatr. 2010;222:321-326

[20] Lillehei CW, Cohen M, Warden HE, Read RC, Aust JB, Dewall RA, Varco RL. Direct vision intracardiac surgical correction of the tetralogy of fallot, pentalogy of fallot, and pulmonary atresia defects; report of first ten cases. Ann Surg. 1955;142:418-442

[21] Gummert JF, Funkat A, Beckmann A, Schiller W, Hekmat K, Ernst M, Haverich A. Cardiac surgery in germany during 2008. A report on behalf of the german society for thoracic and cardiovascular surgery. Thorac Cardiovasc Surg. 2009;57:315-323

[22] Bertranou EG, Blackstone EH, Hazelrig JB, Turner ME, Kirklin JW. Life expectancy without surgery in tetralogy of fallot. Am J Cardiol. 1978;42:458-466

[23] Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol. 1997;30:1374-1383

[24] Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of fallot: A multicentre Surveillance. Lancet. 2000;356:975-981

[25] Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of fallot. Restrictive physiology predicts superior exercise performance. Circulation. 1995;91:1775-1781

[26] Gatzoulis MA, Elliott JT, Guru V, Siu SC, Warsi MA, Webb GD, Williams WG, Liu P, McLaughlin PR. Right and left ventricular systolic function late after repair of tetralogy of fallot. Am J Cardiol. 2000;86:1352-1357

[27] Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of fallot. Qrs prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation. 1995;92:231-237

[28] Silversides CK, Kiess M, Beauchesne L, Bradley T, Connelly M, Niwa K, Mulder B, Webb G, Colman J, Therrien J. Canadian cardiovascular society 2009 consensus conference on the management of adults with congenital heart disease: Outflow tract obstruction, coarctation of the aorta, tetralogy of fallot, ebstein anomaly and marfan's syndrome. Can J Cardiol. 2010;26:e80-97

[29] Oosterhof T, van Straten A, Vliegen HW, Meijboom FJ, van Dijk AP, Spijkerboer AM, Bouma BJ, Zwinderman AH, Hazekamp MG, de Roos A, Mulder BJ. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of fallot using cardiovascular magnetic resonance. Circulation. 2007;116:545-551

[30] Cheung EW, Wong WH, Cheung YF. Meta-analysis of pulmonary valve replacement after operative repair of tetralogy of fallot. Am J Cardiol. 2010;106:552-557

[31] Oosterhof T, Mulder BJ, Vliegen HW, de Roos A. Cardiovascular magnetic resonance in the follow-up of patients with corrected tetralogy of fallot: A review. Am Heart J. 2006;151:265-272

[32] Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part i: Anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation. 2008;117:1436-1448

[33] Adamson L, Vohra HA, Haw MP. Does pulmonary valve replacement post repair of tetralogy of fallot improve right ventricular function? Interact Cardiovasc Thorac Surg. 2009;9:520-527

Annex 1. List of stand-alone documents

#	Document Reference Number	Date	Title
1	Appendix 01	xx.11.2013	Example for a Patient Information Sheet
2	Appendix 02	xx.11.2013	Example for an Executive Patient Information Sheet
3	Appendix 03	xx.11.2013	Example for a Short Patient Information Sheet
4	Appendix 04	xx.11.2013	Example for an Informed Consent Form to the processing of personal data
5	Appendix 05	xx.11.2013	Surveillance Parameters
6	Appendix 06	xx.11.2013	Case Report Form
7	Appendix 07	as amended	Product Liability Insurance
8	Appendix 08	as amended	Investigators contact list

Annex 2. ENCePP checklist for study protocols

Annex 3. Additional Information

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Appendix 01

Example[1] for a Patient Information Sheet to participate in the European clinical Study for the Application of regenerative heart valves – ESPOIR

(the "Surveillance")

INTRODUCTION

Dear patient, dear parents,

Your attending physician has asked you whether you/ your child wish to participate in a Surveillance evaluating a novel biological heart valve substitute. Our local ethics committee has reviewed this project and given approval for its implementation.

In order to decide whether or not you wish to be a part of this Surveillance, you should know enough about the risks and benefits of the Surveillance to make an informed decision. This consent form gives you detailed information, which a member of the clinical team will discuss with you. This discussion will include all of the important aspects of this Surveillance such as the purpose of the Surveillance, the procedures that will be performed, any risks and possible benefits. Once you understand the Surveillance, you will be asked if you wish to participate. If you agree to participate in this Surveillance, you will be asked to sign this form.

WHAT IS THE PURPOSE OF THE SURVEILLANCE?

As you know from your attending physician, it will be necessary to replace your /or your child's pulmonary heart valve in the near future. There are different implants available which can be used to carry out this replacement.

As a result of your discussions with your attending physician, you decided for a replacement with a decellularized human heart valve (ESPOIR PV).

This is performed via a standardized operation for pulmonary valve replacement using cardio-pulmonary-bypass (heart-lung-machine) as with any other authorized pulmonary valve substitute.

[1] This is only an example of a Patient Information Sheet. Each Surveillance Centre is responsible to ensure that patient information is obtained in full compliance with applicable local laws. Applicable local law may require to ament the language in this example.

In our follow-up examinations, we focus on heart valve function during non-invasive examinations like ultrasound check-up (echocardiography) and cardiac magnetic resonance (MRI). All clinical examinations, both before and after the implantation, will be carried out as in routine care for all patients with congenital heart disease requiring pulmonary valve replacement.

The purpose of this Surveillance is to determine the safety and efficacy of decellularized human heart valves (ESPOIR PV) for surgical replacement of the pulmonary valve in children and adults with congenital heart disease.

We ask you to participate in this Surveillance to collect and to process medical data within standard care to improve the vigilance and safety of ESPOIR PV.

WHAT ARE THE RISKS OF TAKING PART IN THIS SURVEILLANCE?

Your doctor will make every effort to minimize the risks and discomforts of the procedure of heart valve replacement. Most risks and complications can be effectively treated with medications or surgery that can be provided to you at your doctor's decision. Some complications could result in serious injury or death despite additional treatment. In the event of a serious complication or injury, it may be necessary to surgically remove the valve.

As the procedures in this Surveillance do not go beyond the standard care, there are no additional medical risks attached to the Surveillance.

WHAT ARE THE BENEFITS OF TAKING PART IN THIS SURVEILLANCE?

You may or may not personally benefit from participating in this Surveillance. By participating in this Surveillance you may contribute new information, which may benefit patients in the future.

HOW MANY PEOPLE WILL TAKE PART IN THE SURVEILLANCE?

The clinical Surveillance of ESPOIR is conducted at 8 centres in Europe including a total of 200 patients, children and adults, with congenital heart defects. 25 patients will take part in the Surveillance at this hospital.

DO I HAVE TO TAKE PART AND WHAT HAPPENS IF I LEAVE THE SURVEILLANCE?

Your decision to take part is voluntary.

Participation in this Surveillance is completely voluntary. You or your child can decline to participate or withdraw from the Surveillance at any time without the need to provide any reason.

If you decide not to participate in the Surveillance, your rights and treatment will not be affected in any way.

You can withdraw your informed consent to participate in the Surveillance. This will not affect the standard of care you receive, however you will still need to visit the hospital to ensure the valve is still effective, as this is part of the standard care for this type of treatment. The only difference is that no information will be gathered for the purpose of this Surveillance.

As a volunteer in this clinical research Surveillance you will be asked to return for scheduled follow-up visits for safety reasons. In addition, while participating in this Surveillance, you agree not to participate in any investigational studies, including those involving investigational or experimental drugs or other medical devices within one year of your surgical procedure. You also agree to notify your doctor of any address changes that may occur.

WHAT HAPPENS IF THE SURVEILLANCE IS DISCONTINUED?

The competent authorities, the Sponsor or your doctor may terminate your participation without regard to your consent. In this event, your doctor will inform you of any information that may affect you. Any Surveillance-related information collected up to the time you are terminated from the Surveillance will be available for analysis.

Your regular check ups at the hospital will not be affected if the Surveillance is stopped. You will continue to attend hospital for regular procedures and check ups and your valve will continue to be monitored.

WILL I BE PAID TO PARTICIPATE IN THE SURVEILLANCE?

No, you will receive no payment or other recompense for participating in the

Surveillance. No additional costs will arise for you or your health insurance company as a result of participation in this Surveillance.

STATEMENT OF FINANCIAL INTERESTS

This Surveillance is supported by the European Commission (FP7-HEALTH-2011, Grant No. 278453). In addition, the Sponsor is paying the clinic to cover the costs for data processing during the follow-up period. Your attending physician has no financial interests in conducting this Surveillance.

INSURANCE

The product ESPOIR PV, used in this Surveillance, has been approved by the authorities. Insurance coverage is provided by a product liability insurance.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

During the course of this survey, all relevant information about your treatment or that of your child which may affect your opinion on your participation in follow-up examinations in relation to this follow-up examination will be communicated to you. If new findings arise which may influence your willingness to participate in the Surveillance, you will be notified of these findings immediately and provided with a detailed explanation.

WHO IS SPONSORING THE SURVEILLANCE?

Corlife oHG, Feodor-Lynen-Str. 23, D-301625 Hannover (the “Sponsor”) is sponsoring the Surveillance.

ADVERSE REACTIONS

If you believe that you have developed a problem which may be associated with your heart valve replacement, you should contact your attending physician or the medical emergency. Please show your Implant Identification Card to facilitate the identification of the implant.

QUESTIONS ABOUT THE SURVEILLANCE

If you have any questions about the Surveillance, you should contact the team at your Clinic. If you have questions about your rights as a research subject, you should contact the Ethics Committee (Insert EC Number). The Ethics Committee for this Surveillance site is Insert Surveillance EC Name and the Chairperson is Insert EC Chair Name).

INFORMED CONSENT

If you agree to participate/to your child's participation in this follow-up examination, please sign the enclosed consent form. One copy is for you to keep for your records.

With best wishes for you - your child and you

Appendix 02

Example[1] for an Executive Patient Information Sheet to participate in the European clinical Study for the Application of regenerative heart valves

(the "Surveillance")

INTRODUCTION

Dear patient,

Your attending physician has asked you whether you wish to participate in a Surveillance evaluating a novel biological heart valve substitute. Our local ethics committee has reviewed this project and given approval for its implementation.

In order to decide whether or not you wish to be a part of this Surveillance, you should know enough about the Surveillance to make an informed decision. This consent form gives you detailed information, which a member of the clinical team will discuss with you. This discussion will include all of the important aspects of this Surveillance. Once you understand the Surveillance, you will be asked if you wish to participate. If you agree to participate in this Surveillance, you will be asked to sign this form.

WHAT IS THE PURPOSE OF THE SURVEILLANCE?

As you know from your attending physician, it will be necessary to replace your pulmonary heart valve in the near future. There are different implants available which can be used to carry out this replacement.

As a result of your discussions with your attending physician, you decided for a replacement with a decellularized human heart valve (ESPOIR PV).

The purpose of this Surveillance is to determine the safety and efficacy of decellularized human heart valves (ESPOIR PV) for surgical replacement of the pulmonary valve in children and adults with congenital heart disease.

We ask you to participate in this Surveillance to collect and to process medical

[1] This is only an example of an Executive Patient Information Sheet. Each Surveillance Centre is responsible to ensure that patient information and patient consent is obtained in full compliance with applicable local laws. Applicable local law may require to ament the language in this example.

data within standard care to improve the vigilance and safety of ESPOIR PV.

WHAT ARE THE RISKS OF TAKING PART IN THIS SURVEILLANCE?

Your doctor will make every effort to minimize the risks and discomforts of the procedure of heart valve replacement. Most risks and complications can be effectively treated with medications or surgery that can be provided to you at your doctor's decision. Some complications could result in serious injury or death despite additional treatment. In the event of a serious complication or injury, it may be necessary to surgically remove the valve.

As the procedures in this Surveillance do not go beyond the standard care, there are no additional medical risks attached to the Surveillance.

WHAT ARE THE BENEFITS OF TAKING PART IN THIS SURVEILLANCE?

You may or may not personally benefit from participating in this Surveillance. By participating in this Surveillance you may contribute new information, which may benefit patients in the future.

HOW MANY PEOPLE WILL TAKE PART IN THE SURVEILLANCE?

The clinical Surveillance of ESPOIR is conducted at 8 centers in Europe including a total of 200 patients, children and adults, with congenital heart defects. 25 patients will take part in the Surveillance at this hospital.

DO I HAVE TO TAKE PART AND WHAT HAPPENS IF I LEAVE THE SURVEILLANCE?

Your decision to take part is voluntary.

Participation in this Surveillance is completely voluntary. You or your child can decline to participate or withdraw from the Surveillance at any time without the need to provide any reason.

If you decide not to participate in the Surveillance, your rights and treatment will not be affected in any way.

WILL I BE PAID TO PARTICIPATE IN THE SURVEILLANCE?

No, you will receive no payment or other recompense for participating in the Surveillance. No additional costs will arise for you or your health insurance company as a result of participation in this Surveillance.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

During the course of this survey, all relevant information about your treatment or that of your child which may affect your opinion in relation to this follow-up examination will be communicated. If new findings arise which may influence your willingness to participate in the Surveillance, you will be notified of these findings immediately and provided with a detailed explanation.

ADVERSE REACTIONS

If you believe that you have developed a problem which may be associated with your heart valve replacement, you should contact your attending physician or the medical emergency. Please show your Implant Identification Card to facilitate the identification of the implant.

QUESTIONS ABOUT THE SURVEILLANCE

If you have any questions about the Surveillance, you should contact the team at your Clinic. If you have questions about your rights as a research subject, you should contact the Ethics Committee (Insert EC Number). The Ethics Committee for this Surveillance site is Insert Surveillance EC Name and the Chairperson is Insert EC Chair Name).

INFORMED CONSENT

If you agree to participate/to your child's participation in this follow-up examination, please sign the enclosed consent form. One copy is for you to keep for your records.

With best wishes for you - your child and you

APPENDIX 03

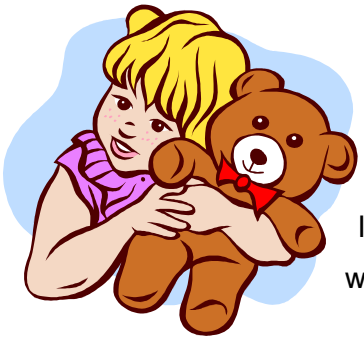
Example[1] for Short Patient Information Sheet to participate in the

European clinical Study for the Application of regenerative heart valves – ESPOIR

(the "Surveillance")

Hi, you came to our hospital as your heart is sick.
That is the reason why you are feeling tired sometimes.

Doctors will repair you heart in an operation.



In the past you already had such an operation and you were feeling much better after this operation.

Your parents will stay with you and look after you all the time.

After the operation doctors will carefully look at your heart very closely using the echo-machine you already know.

We would like to collect information about your disease and evaluate.
All children with the same heart problems are asked whether they want to participate. This is called a surveillance or study.

All children receive the best treatment doctors know at the moment.
If your parents agree you will join this Surveillance.

Do you have any questions for us or for your parents?

[1] This is only an example of a Short Patient Information Sheet. Each Surveillance Centre is responsible to ensure that patient information and patient consent is obtained in full compliance with applicable local laws. Applicable local law may require to ament the language in this example.

APPENDIX 04 - Example[1] for an Informed Consent Form to the processing of personal data in connection with the participation in the EUROPEAN CLINICAL STUDY FOR THE APPLICATION OF REGENERATIVE HEART VALVES – ESPOIR
(the "Surveillance")

Dear patient, dear parents,

you agreed that you/your child participates in the Surveillance ESPOIR in the course of which we will monitor the healing process in connection with your/your child's treatment with a novel biological heart valve substitute that has been approved for medical treatment (the "Surveillance"). In this context, it will be necessary to collect, process, and use certain personal data of you/your child.

Protecting your/your child's privacy is an important part of the Surveillance. With this document we would like to inform you about the collection and use of your/your child's personal data in connection with your/your child's medical treatment and the Surveillance and ask you for your consent to the collection, processing, and use of your personal data as outlined in this document.

Providing your consent is absolutely voluntary. If you provide your consent, a copy of your consent will be kept in your health record.

WHO WILL HAVE ACCESS TO MY/MY CHILD'S DATA?

The following persons will see your health and Surveillance records that identify you/your child by name:

- the treating physicians, the nursing and administration staff at our hospital in connection with your medical treatment, the monitoring of your treatment and healing process, and administrative matters
- the Ethical Committee located at our hospital upon their request;
- the competent health authorities upon their request

The following persons will only see your/your child's health data in an anonymized fashion that does not allow your/your child's personal identification:

[1] This is only an example of an Informed Consent Form. Each Surveillance Centre is responsible to ensure that patient information and patient consent is obtained in full compliance with applicable local laws. Applicable local law may require to ament the language in this example.

- the Sponsor of the Surveillance and persons working with the Sponsor
- the Principal Investigator and the Study Director of the Surveillance
- the Surveillance monitor
- the Ethics and Governance Counsel

The Sponsor of the Surveillance is the German company “corlife OHG” which is responsible for the quality of the implant. The Principal Investigator is Dr. Haverich of the Hannover Medical School who is responsible for quality and coordination of the Surveillance. The Study Director, Dr. Samir Sarikouch, is responsible for the scientific analysis. The Surveillance Monitor will be working with the research team at our hospital to ensure that your treating physician records your health data in a legible and structured fashion so that it is suitable for scientific analysis. The Ethics and Governance Counsel has assumed the responsibility for periodically reviewing and evaluating accumulated Surveillance data to ensure participant safety.

WHAT DATA WILL BE COLLECTED?

Your treating physician will collect the following information about you/your child:

- name
- initials
- address
- date of birth
- age
- sex
- medical condition
- physical condition
- medications
- the results of medical tests and procedures you had before the Surveillance
- the results of medical tests and procedures during the Surveillance

Your/your child’s treating physician and our hospital personnel will collect and

use your/your child's personal and medical data only in a scope required for your/your child's medical treatment and for purposes of monitoring the healing progress in connection with the Surveillance. You may ask your treating physician to see the data that has been collected about you/your child.

Your/your child's name and contact information will be kept secure by us and will not be shared with persons other than hospital personnel without your permission.

HOW IS MY/MY CHILD'S DATA RECORDED? HOW IS MY/MY CHILD'S DATA ANONYMIZED?

Your treating physician and his/her team will collect your/your child's personal and medical data mentioned above only in a scope necessary for your/your child's medical treatment. It is within the discretion of your treating physician to decide which information/data your treating physician requires for your/your child's medical treatment. In order to ensure a consolidated quality of data for purposes of the Surveillance, your treating physician has been provided with a so-called Case Report Form (CRF) that is meant to assist your treating physician in recording your medical data.

Your treating physician is not allowed to enter any data on the CRF that would allow to identify you/your child by name. Rather, the your treating physician or his team will anonymize your data to be recorded on a CRF by assigning to you/your child a three-digit patient identification number that must consist of a combination of letters and numbers. Only your treating physician and members of his/her team will be able to assign your/your child's name to your/your child's patient identification number.

Only the patient identification number will be recorded on a CRF.

FOR WHAT PURPOSE IS MY/MY CHILD'S DATA COLLECTED?

Your/your child's treating physician and personnel at our hospital will only collect, process, and use information they need for your/your child's medical treatment with an ESPOIR PV and the monitoring of the healing process. In addition, your/your child's anonymized medical data only will be used by the research team for purposes of this Surveillance. In connection with the Surveillance, the Principal Investigator will analyze and compare your/your child's anonymized medical data with the anonymized medical

data from the other participants in the Surveillance. Your/your child's personal and medical data will not be used for any other purposes.

WHO ELSE WILL HAVE ACCESS TO MY/MY CHILD'S DATA?

Your/your child's medical data recorded on a CRF will be sent to the Sponsor for analysis. The information on a CRF will be anonymized since a CRF will only contain your/your child's patient identification number. The Sponsor will not be able to identify you/your child by name on the basis of the patient information number. The anonymized medical data contained in the CRFs will also be disclosed to the Principal Investigator, the Study Director, the Surveillance monitor, and the Ethical Governance Board.

As mentioned above, the Surveillance monitor may have access to the data contained in your/your child's CRF for purposes of ensuring that your/your child's medical data is accurately reported on the CRFs.

For purposes of the Surveillance, the Ethical Governance Council has assumed the responsibility of monitoring data accuracy for patient safety. The Ethical Governance Council will only have access to anonymized data contained in the CRF.

WILL MY/MY CHILD'S DATA BE PUBLISHED?

Your/your child's name and contact information will be kept secure by the Surveillance doctor and the hospital personnel. It will not be shared with others without your permission. The results of the Surveillance will be reported to the European Commission and published in a scientific publication. These reports/publications, however, will neither mention your/your child's name other data that would allow your/your child's identification, nor identify our hospital. Your/your child's name will not appear in any report or article published as a result of this Surveillance.

FOR HOW LONG WILL YOU KEEP MY/MY CHILD'S DATA?

Information collected for this Surveillance, including your/your child's personal and medical data will be kept as long as required by applicable law. This period could be 15 years or more.

Unless you withdraw your consent, after the Surveillance related to you/your child has ended, your/your child's treating physician or his or her successor may want to continue reviewing your/your child's health records since we may want to follow-up with your/your child's progress and to verify whether the medical data collected by your treating physician.

CAN I WITHDRAW MY CONSENT?

You have the right to withdraw your consent to the collection, processing, and use of your/your child's personal data (e.g., name, address) and/or medical data (all data related to your/your child's medical condition) at any time. If you withdraw your consent to the use of your/your child's personal data, the hospital may have to discontinue your medical treatment, since the hospital would not be allowed anymore to use your/your child's personal data.

You can also choose to withdraw your consent to the collection, processing and use of your/your child's medical data at any time. This will not affect the standard of care you receive, however, you will still need to visit the hospital to ensure the valve is still effective, as this is part of the standard care for this type of treatment. The only difference is that no personal medical data will be collected for purposes of this Surveillance anymore.

Your/your child's anonymized medical data, however, does not qualify for personal data pursuant to applicable data protection laws. Therefore, if you withdraw your consent, anonymized medical data collected up to that time may continue to be used by the research team.

YOUR CONSENT TO THE COLLECTION, PROCESSING, USE, AND TRANSFER OF YOUR/YOUR CHILD'S PERSONAL DATA

I have read and understood the above explanations on the collection, processing, and use of my/my child's personal data in connection with my/my child's medical treatment and my/my child's participation in the Surveillance.

I hereby consent to the collection, processing, and use of my/my child's personal and medical data by the treating physicians and the hospital's personnel for the purposes of my/my child's medical treatment. I consent to the disclosure of my/my

child's personal and medical data to the competent regulatory agencies in the health sector upon their request. I also consent to the collection, processing, and use of my/my child's medical data as described in this document for purposes of monitoring my/my child's healing process in the course of the Surveillance. Further, I consent to the anonymization of my/my child's medical data and the processing of such anonymized data by the Sponsor, the Principle Investigator, and the Study Director, the Surveillance monitor, and the Ethical Governance Council for purposes of the Surveillance. I also consent to the disclosure of my/my child's personal data and medical data to the Ethical Committee for purposes of evaluating my/my child's participation in the Surveillance from an ethical perspective. I understand that I can withdraw my consent to the collection, processing, and use of my/my child's personal and medical data at any time.

	Name (printed)	Signature	Date
Participant[2]			
Participant´s Authorized Legal Representative			
Participant´s Authorized Legal Representative			
Witness			

[2] All participants who are capable of discernment shall sign the informed consent form, e.g. also minors.

Appendix 05 - Surveillance parameters

Baseline: Patient data at Surveillance entrance		
Surveillance center	1 Medizinische Hochschule Hannover (MHH) 2 Universitatea de Stat de Medicina si Farmacie “Nicolae Testemitanu” (SMPHU) 3 Leids Universitair Medisch Centrum (LUMC) 4 Great Ormond Street Hospital for Children (GOSH) 5 Università degli Studi di Padova (UNIPD) / Azienda Ospedaliera Di Padova (AOP) 6 Université Paris Descartes (UPD) 7 Universität Zürich (UZH) 8 University Hospital Gasthuisberg Leuven (K.U.Leuven)	please complete
patient No.	Randomly created without application of any system or coding mechanism.	please complete
Informed consent executed	no, yes	please tick one
date of signature	e.g. 01.02.1900	please complete
Inclusion criteria	no, yes	please tick one
exclusion criteria	no, yes	please tick one
Month, year of birth	e.g. Oct.1999	please tick & complete
sex	male, female, other	please tick one
blood group	A, B, AB, 0, unknown	please tick one
Rhesus factor	positive, negative, unknown	please tick one
basic malformation	Tetralogy of Fallot, Pulmonary Stenosis (isolated), PA/VSD, PA/IVS, DORV, Aortic stenosis/regurgitation – ROSS-Procedure, TGA, other	please tick one
associated malformations	none, chromosomal aberrations, musculo-sceletal, neurological, other	please tick one
other non-cardiac, serious	no, yes	please tick one

Baseline: Patient data at Surveillance entrance		
disease		
number of previous operations, in total	0,1,2,3,4,5,>5	please tick one
number of previous heart lung machine operations	0,1,2,3,4,5,>5	please tick one
number of previous pulmonary valve replacements	0,1,2,3,>3	please tick one
type of last RV-PA conduit	native, Dacron/Gore Tex tube, aortic homograft, pulmonary homograft, Contregra®, Melody®, Hancock, Carpentier-Edwards, Matrix P, other	please tick one
reason for pulmonary valve replacement (PVR)	regurgitation, stenosis, regurgitation and stenosis, tricuspid regurgitation, ventricular dilatation/heart failure, arrhythmia, other	please tick all applicable
date of physical examination	e.g. 01.02.1900	please complete
height	e.g. 173 cm	please complete
weight	e.g. 84 cm	please complete
heart rate (resting)	in beats per min	please complete
blood pressure	in mmHg, e.g. 120/60	please complete
NYHA classification	I, II, III, IV, V	please tick one
medication	none, platelet inhibitors, warfarin, ß-blocker, other	please tick all applicable
clinical signs of haemolysis (white blood cells, free hemoglobin, haptoglobin, CRP, LDH)	other unit	please complete
	value	please complete
	evaluation: normal, abnormal	please tick one
clinical signs of arrhythmia	none, mid / moderate / severe ventricular extraystolia, others	please tick one

Echocardiography at Surveillance entrance, discharge, 3, 6, 2, 24 months		
Surveillance center	1 Medizinische Hochschule Hannover (MHH) 2 Universitatea de Stat de Medicina si Farmacie “Nicolae Testemitanu” (SMPHU) 3 Leids Universitair Medisch Centrum (LUMC) 4 Great Ormond Street Hospital for Children (GOSH) 5 Università degli Studi di Padova (UNIPD) / Azienda Ospedaliera Di Padova (AOP) 6 Université Paris Descartes (UPD) 7 Universität Zürich (UZH) 8 University Hospital Gasthuisberg Leuven (K.U.Leuven)	please complete
patient No.	Randomly created without application of any system or coding mechanism.	please complete
occaison	baseline, discharge 3 months follow-up, 6 months follow-up, 12 months follow-up, other	please tick one
date of echocardiography	e.g. 01.02.1900	please complete
right atrial dilatation	yes, no	please tick one
left atrial dilatation	yes, no	please tick one
tricuspid regurgitation	mild, moderate, severe	please tick one
tricuspid regurgitation	max. velocity in (m/sec)	please complete
mitral regurgitation	mild, moderate, severe	please tick one
mitral regurgitation	max. velocity in (m/sec)	please complete
left/right ventricular enddiastolic diameter	in (mm)	please complete
left/right ventricular endsystolic diameter	in (mm)	please complete
left/right ventricular function	normal, mildly reduced, severely reduced	please tick one
pulmonary/aortic valve, diameter	in (mm)	please complete
pulmonary/aortic valve	velocity in (m/sec)	please complete

Echocardiography at Surveillance entrance, discharge, 3, 6, 2, 24 months		
PW-doppler	mean gradient in (mmHg)	please complete
	max. gradient in (mmHg)	please complete
pulmonary/aortic valve CW-doppler	velocity in (m/sec)	please complete
	mean gradient in (mmHg)	please complete
	max. gradient in (mmHg)	please complete
pulmonary/aortic regurgitation	none, trace, mild, mild-moderate, moderate, moderate-severe, severe	please tick one
calcification	nes, no	please tick one
leaflets		
right/left ventricular outflow PW-doppler	velocity in (m/sec)	please complete
	mean gradient in (mmHg)	please complete
	max. gradient in (mmHg)	please complete
Right/left pulmonary artery	velocity in (m/sec)	please complete

MRI at Surveillance entrance and after 12, 24 months		
	Required MRI sequences: cine volume stack for volumetric analysis, cine sagittal and coronal acquisition delineating pulmonary valve function, phase-contrast flow measurements in main pulmonary artery and aorta ascendens	
	**to be analyzed by the MRI Core Laboratory at MHH (Section 8.1):**	
Surveillance center	1 Medizinische Hochschule Hannover (MHH) 2 Universitatea de Stat de Medicina si Farmacie “Nicolae Testemitanu” (SMPHU) 3 Leids Universitair Medisch Centrum (LUMC) 4 Great Ormond Street Hospital for Children (GOSH) 5 Università degli Studi di Padova (UNIPD) / Azienda Ospedaliera Di Padova (AOP) 6 Université Paris Descartes (UPD) 7 Universität Zürich (UZH) 8 University Hospital Gasthuisberg Leuven (K.U.Leuven)	please complete
patient No.	Randomly created without application of any system or coding mechanism.	please complete
occaison	baseline, 12 months follow-up, other	please tick one
date of MRI scan	e.g. 01.02.1900, as indicated on mini DVD	please complete
right/left ventricular enddiastolic volume	in (ml/m^2)	please complete
right/left ventricular endsystolic volume	in (ml/m^2)	please complete
right/left ventricular mass	in (g/m^2)	please complete
pulmonary artery / aorta ascendens flow	max. velocity in (m/sec)	please complete
	regurgitation in (%)	please complete
pulmonary/aortic valve diameter	diameter (mm)	please complete
	proximal stenosis (yes/no)	please tick one

MRI at Surveillance entrance and after 12, 24 months		
	distal stenosis (yes/no)	please tick one
	valvular stenosis (yes/no)	please tick one

Implantation		
Surveillance center	1 Medizinische Hochschule Hannover (MHH) 2 Universitatea de Stat de Medicina si Farmacie “Nicolae Testemitanu” (SMPHU) 3 Leids Universitair Medisch Centrum (LUMC) 4 Great Ormond Street Hospital for Children (GOSH) 5 Università degli Studi di Padova (UNIPD) / Azienda Ospedaliera Di Padova (AOP) 6 Université Paris Descartes (UPD) 7 Universität Zürich (UZH) 8 University Hospital Gasthuisberg Leuven (K.U.Leuven)	please complete
patient No.	Randomly created without application of any system or coding mechanism.	please complete
Lot.-Nr.	e.g. corHVP-2012-0015	please complete
blood-group (donor)	A, B, AB, 0, unknown	please tick one
rhesus factor (donor)	positive, negative, unknown	please tick one
diameter	e.g. 19 mm	please complete
Inside-logger	please send back to corlife, Feodor-Lynen-Str. 23, D-30615 Hannover	
date of implantation	e.g. 01.02.1900	please complete
operation time, total	e.g. 03:45 (hours:min)	please complete
extracorporeal circulation	e.g. 104 (min)	please complete
aortic cross clamp time	e.g. 104 (min)	please complete
name of surgeon		please complete
concomitant procedures	none, PA-augmentation, RPA-augmentation, LPA augmentation, other	please tick all applicable
augmentation material	none, Dacron, native pericardium, treated pericardium, other	please tick all applicable

Implantation		
glue	none, proximal, distal, RPA, LPA, other	please tick all applicable
continuous suture	none, proximal, distal, RPA, LPA, other	please tick all applicable
adverse reaction	intra and postoperative complications in ICU	please tick all applicable, please submit SAR Report if applicable

Follow-up: discharge and any follow-up visit		
Surveillance center	1 Medizinische Hochschule Hannover (MHH) 2 Universitatea de Stat de Medicina si Farmacie “Nicolae Testemitanu” (SMPHU) 3 Leids Universitair Medisch Centrum (LUMC) 4 Great Ormond Street Hospital for Children (GOSH) 5 Università degli Studi di Padova	please complete

	(UNIPD) / Azienda Ospedaliera Di Padova (AOP) 6 Université Paris Descartes (UPD) 7 Universität Zürich (UZH) 8 University Hospital Gasthuisberg Leuven (K.U.Leuven)	
patient No.	Randomly created without application of any system or coding mechanism.	please complete
occaison	discharge 3 months follow-up, 6 months follow-up, 12 months follow-up, other	please tick one
date of visit	e.g. 01.02.1900	please complete
height	e.g. 173 cm	please complete
weight	e.g. 84 cm	please complete
heart rate (resting)	in beats per min	please complete
blood pressure	in mmHg, e.g. 120/60	please complete
NYHA classification	I, II, III, IV, V	please tick one
medication	none, platelet inhibitors, warfarin, ß-blocker, diuretics, digoxin/digitoxin, other	please tick all applicable
adverse reaction	postoperative complications	please tick all applicable, please submit SAR Report if applicable

Re-operation or Catheter intervention		
Surveillance center	1 Medizinische Hochschule Hannover (MHH) 2 Universitatea de Stat de Medicina si Farmacie “Nicolae Testemitanu” (SMPHU) 3 Leids Universitair Medisch Centrum (LUMC) 4 Great Ormond Street Hospital for Children (GOSH)	please complete

Re-operation or Catheter intervention		
	5 Università degli Studi di Padova (UNIPD) / Azienda Ospedaliera Di Padova (AOP) 6 Université Paris Descartes (UPD) 7 Universität Zürich (UZH) 8 University Hospital Gasthuisberg Leuven (K.U.Leuven)	
patient No.	Randomly created without application of any system or coding mechanism.	please complete
date of re-operation	e.g. 01.02.1900	please complete
type of reoperation	explantation of Espoir pv / implantation of new valve, patch plasty, other	please tick one
reason for reoperation	stenosis, regurgitation, endocarditis, other	please tick all applicable
date of intervention	e.g. 01.02.1900	please complete
type of intervention	ballondilatation, percutaneous valve implantation, stent implantation, other	please tick one
reason for intervention	stenosis, regurgitation, endocarditis, other	please tick all applicable

European clinical study for the application of regenerative heart valves

Case Report Form 2013-11,06.11.13

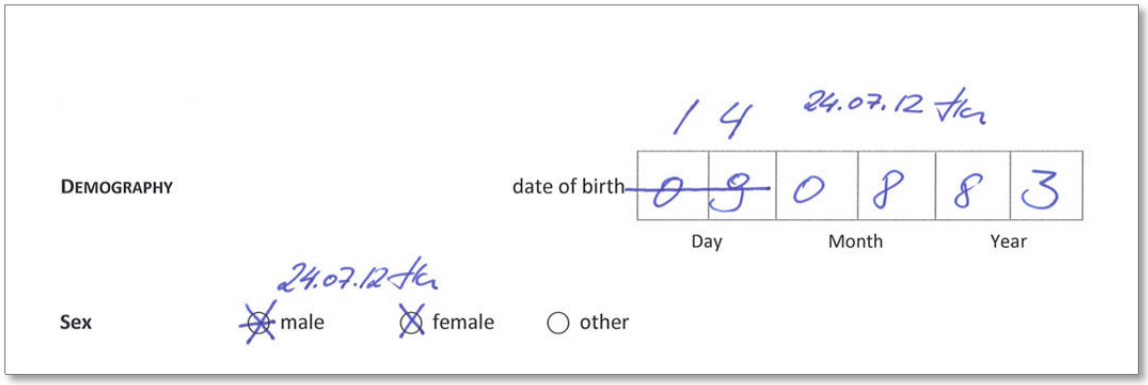
ENCePP Study Ref. Number 5064] ClinicalTrials.gov NCT 02 035 540

E·S·P·  ·I·R

corlife oHG Feodor-Lynen-Str. 23 D-30625 Hannover Germany
06.11.2013

Register: Baseline / … / Discharge

Instructions for completing Case Report Form



E·S·P·  ·I·R

Center		Patient N°		

Baseline	Page 1/4

Create a "Patient N°" by random combination of capital letters and numbers. Do not use numbers or letters related to your patient (e.g., name initials or part of birth date).

INCLUSION CRITERIA

(1) Informed consent form, signed by patient and/or legal representative

◯ no ◯ yes

Date of signature

Day		Month		Year	

(2) Indication for pulmonary valve replacement according to current medical guidelines in congenital heart disease

◯ no ◯ yes

EXCLUSION CRITERIA

(1) The patient has <u>not</u> provided informed consent.

◯ no ◯ yes

(2) The patient suffers from generalized connective tissue disorders (eg, Marfan syndrome), or active rheumatic disorders or severe asymmetric calcification of the valve ring. The coronary arteries of the patient are in abnormal position or heavily calcified.

◯ no ◯ yes

(3) Hypersensitivity against sodium dodecyl sulphate (SDS), sodium desoxycholate (SDC), human collagen (or other elastic fibers) or Benzonase®

◯ no ◯ yes

Patient is only eligible for the study, if all inclusion criteria are fulfilled (i.e. answered with YES) <u>and</u> no exclusion criteria are met (i.e. all answered with NO)

The decision to treat the patient with ESPOIR PV is independent from participation in this study.

E·S·P·  ·I·R

Center Patient N°

Baseline	Page 2/4

Date of birth ◯ Jan ◯ Feb ◯ Mar ◯ Apr ◯ May ◯ Jun ◯ Jul ◯ Aug ◯ Sep ◯ Oct ◯ Nov ◯ Dec

Year

Sex ◯ male ◯ female ◯ other

Blood group ◯ A ◯ B ◯ AB ◯ O ◯ unknown

Rhesus factor ◯ positive ◯ negative ◯ unknown

MEDICAL HISTORY

Basic cardiac malformation *(please tick only one)*

◯ Tetralogy of Fallot

◯ Aortic stenosis/regurgitation-ROSS-Procedure

◯ Pulmonary Atresia with Septal Defect (PA-VSD)

◯ Pulmonary Stenosis (isolated)

◯ Pulmonary Atresia with Intact Ventricular Septum (PA-IVS)

◯ Double Outlet Right Ventricle (DORV)

◯ Pulmonary Atresia with TGA (Transposition of the Great Arteries)

◯ other *(please specify)*

Associated malformations

◯ none

◯ musculoskeletal

◯ other *(please specify)*

◯ chromosomal aberrations

◯ neurological

Other non-cardiac serious disease

◯ no

◯ yes (please specify)

Previous cardiac surgeries

Number of previous cardiac surgeries (including shunt operations):

◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ >5

Number of previous heart-lung machine operations:

◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ >5

Number of previous pulmonary valve replacements:

◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ >3

Type of *previous* pulmonary valve replacement conduit:

◯ Aortic homograft
◯ Pulmonary homograft
◯ Hancock
◯ Melody®
◯ Sapien-Edwards
◯ Contegra®
◯ Carpentier-Edwards Conduit
◯ Matrix P
◯ Dacron/Goretex unvalved conduit
◯ other *(please specify)*

Reason for pulmonary valve replacement (PVR)
(please tick all relevant)

◯ regurgitation
◯ tricuspid regurgitation
◯ stenosis
◯ ventricular
◯ dilatation/heart failure
◯ arrhythmia
◯ other *(please specify)*

Remarks:

E·S·P·  ·I·R

Center | Patient N°

Baseline	Page 4/4

Physical Examination Date of visit ____ ____ ____ ____ ____ ____
Day Month Year

Height ____ ____ ____ cm Weight ____ ____ ____ kg

Heart rate (resting) ____ ____ ____ beats/min

Blood pressure ____ ____ ____ / ____ ____ ____ mmHg
systolic diastolic

NYHA Classification ◯ I ◯ II ◯ III ◯ IV ◯ unknown

Medication ◯ none ◯ platelet inhibitors ◯ Warfarin ◯ ß-Blockers
◯ diuretics ◯ others *(please specify)*

Clinical signs of <u>haemolysis</u> available at current visit ◯ none ◯ yes *(please specify ↙)*

	Unit	other Unit *(please specify)*	Value	Evaluation normal	abnormal
white blood cells	10^3/µl			◯	◯
free hemoglobin (plasma)	g/dl			◯	◯
haptoglobin	g/l			◯	◯
CRP	mg/l			◯	◯
LDH	U/l			◯	◯

Clinical signs of <u>arrhythmia</u> available at current visit ◯ none

ventricular extrasystolia ◯ mild ◯ moderate ◯ severe

◯ others *(please specify)*

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.	white, blue: corlife; yellow: study center
	Version 10/2013

E·S·P·O·I·R

Center | Patient N°

Echocardiography

Page 1/2

◯ Baseline ◯ Discharge ◯ 3 | ◯ 6 | ◯ 12 | ◯ Months

◯ **no echocardiography has been performed**

Date of examination: Day / Month / Year

Right atrial dilatation ◯ yes ◯ no

Left atrial dilatation ◯ yes ◯ no

Tricuspid regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Mitral regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Right ventricle
diameter end-diastolic mm
diameter end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Left ventricle
end-diastolic mm
end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Pulmonary valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

Aortic valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

E·S·P·O·I·R

Center | Patient N°

Echocardiography			Page 2/2
◯ **Baseline**	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Pulmonary regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Aortic regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Calcification ◯ yes ◯ no

Calcification ◯ yes ◯ no

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Right ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Right pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Remarks

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

Center Patient N°

MRI			Page 1/1
◯ **Baseline**	◯ **12 months follow-up**	◯ **other:**	

◯ **there was no MRI performed**

Date of MRI examination

Day Month Year

[Date]	*[Name]*	*[Signature]*

	Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.	white, blue: corlife; yellow: study center
		Version 10/2013

E·S·P·O·I·R

Center | Patient N°

MRI			Page 1/1
◯ Baseline	◯ 12 months follow-up	◯ other:	

date of MRI examination as indicated on disc: Day | Month | Year

Right ventricular volume

end-diastolic . ml/m²

end-systolic . ml/m²

Left ventricular volume

end-diastolic . ml/m²

end-systolic . ml/m²

Right ventricular mass

. g/m²

Left ventricular mass

. g/m²

Pulmonary artery flow

max. velocity . m/s

regurgitation . %

Aorta ascendens flow

max. velocity . m/s

regurgitation . %

Pulmonary valve diameter mm

proximal stenosis ◯ yes ◯ no

distal stenosis ◯ yes ◯ no

valvular stenosis ◯ yes ◯ no

Aortic valve diameter mm

proximal stenosis ◯ yes ◯ no

distal stenosis ◯ yes ◯ no

valvular stenosis ◯ yes ◯ no

Remarks:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, yellow: corlife; yellow: blue center

Version 10/2013

E·S·P·  ·I·R

Center		Patient N°		

Implantation	Page 1/2

IMPLANT ESPOIR PV *(→ information can be taken from delivery note)*

Lot-Nr. corlife: corHVP - 2 0 1 | - | | | | | Diameter: | | mm

Importing tissue bank, Lot-Nr. (if applicable):

Blood group ◯ A ◯ B ◯ AB ◯ O ◯ unknown

Rhesus ◯ positive ◯ negative ◯ unknown

Reminder: 

please send back "inside logger" to
corlife oHG · Feodor-Lynen-Str. 23 · D-30625 Hannover ◯ done

IMPLANTATION

date of implantation: | | | | | | | (day / month / year)

operation time: | | : | | | (hours : minutes)

extracorporeal circulation: | | | | min

aortic cross clamp time: | | | | min

name of surgeon:

Concomitant procedures

◯ none

◯ augmentation of the ...

- ◯ ... pulmonary artery
- ◯ ... pulmonary right artery
- ◯ ... pulmonary left artery

◯ other *(please specify)*

Augmentation material

◯ none

◯ native pericardium

◯ other *(please specify)*

◯ Dacron

◯ treated pericardium

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

E·S·P·  ·I·R

Center Patient N°

Implantation	Page 2/2

Glue

◯ no

◯ yes *(please specify)*

Name: ----------

◯ proximal ◯ distal

◯ right pulmonary artery ◯ left pulmonary artery

◯ other *(please specify)*

Continuous suture

◯ no

◯ yes *(please specify)*

◯ proximal ◯ distal

◯ right pulmonary artery ◯ left pulmonary artery

◯ other *(please specify)*

Adverse Reaction

◯ no

◯ yes *(please specify below;*
if more than one adverse reaction: please add additional pages)

related to ESPOIR PV ◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved

◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention

Additional information concerning adverse reaction:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

corlife oHG
CRF Espoir
Feodor-Lynen-Str. 23

D-30625 Hannover
Allemagne/Germany

Short Message

○ CRF
○ DVD
○ Other: _____

_____

Date: _____

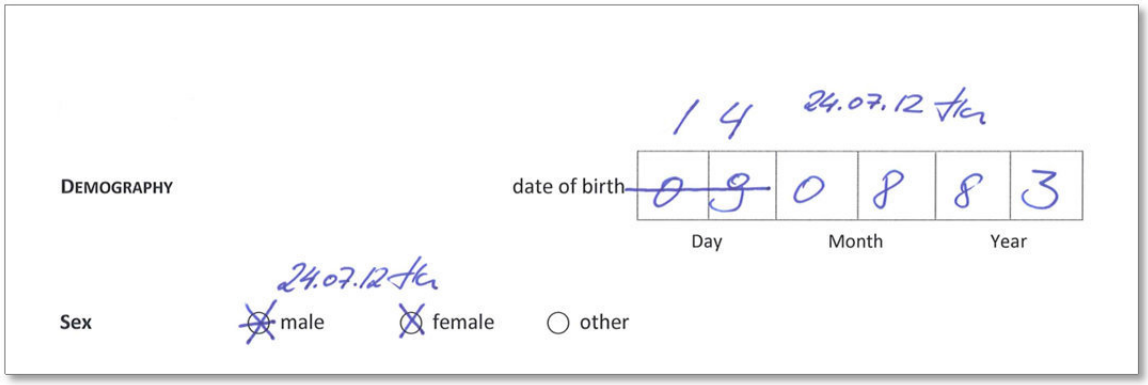
Name: _____

Signature: _____

Stamp:

Register: 3 Months

Instructions for completing Case Report Form



E·S·P·O·I·R

Center | Patient N°

Physical Examination			Page 1/2
	◯ Discharge	◯ 3 | ◯ 6 | ◯ 12 | ◯ Months	

Physical Examination Date of visit (Day / Month / Year)

Height ___ cm Weight ___ kg

Heart rate (resting) ___ beats/min

Blood pressure ___ (systolic) / ___ (diastolic) mmHg

NYHA Classification ◯ I ◯ II ◯ III ◯ IV ◯ unknown

Medication ◯ none ◯ platelet inhibitors ◯ Warfarin ◯ ß-Blockers ◯ others *(please specify)*

Clinical signs of haemolysis available at current visit ◯ none ◯ yes *(please specify ↙)*

	Unit	other Unit *(please specify)*	Value	Evaluation normal	Evaluation abnormal
white blood cells	10^3/µl			◯	◯
free hemoglobin (plasma)	g/dl			◯	◯
haptoglobin	g/l			◯	◯
CRP	mg/l			◯	◯
LDH	U/l			◯	◯

Clinical signs of arrhythmia available at current visit ◯ none ◯ others *(please specify below)*

ventricular extrasystolia ◯ mild ◯ moderate ◯ severe

Additional information:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

Center Patient N°

Physical Examination			Page 2/2
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Adverse Reaction ◯ no

◯ yes *(please specify below;*
if more than one adverse reaction: please add additional pages)

related to ESPOIR PV ◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved ◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention *(Annex A)*

Additional information concerning adverse reaction:

[Date]	*[Name]*	*[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·O·I·R

Center | Patient N°

Echocardiography

Page 1/2

◯ Baseline ◯ Discharge ◯ 3 | ◯ 6 | ◯ 12 | ◯ Months

◯ **no echocardiography has been performed**

Date of examination: Day / Month / Year

Right atrial dilatation ◯ yes ◯ no

Left atrial dilatation ◯ yes ◯ no

Tricuspid regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Mitral regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Right ventricle
diameter end-diastolic mm
diameter end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Left ventricle
end-diastolic mm
end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Pulmonary valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

Aortic valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

E·S·P·O·I·R

Center | Patient N°

Echocardiography			Page 2/2
◯ **Baseline**	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Pulmonary regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Aortic regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Calcification ◯ yes ◯ no

Calcification ◯ yes ◯ no

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Right ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Right pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Remarks

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

corlife oHG
CRF Espoir
Feodor-Lynen-Str. 23

D-30625 Hannover
Allemagne/Germany

Short Message

○ CRF
○ DVD
○ Other: _____

_____

Date: _____

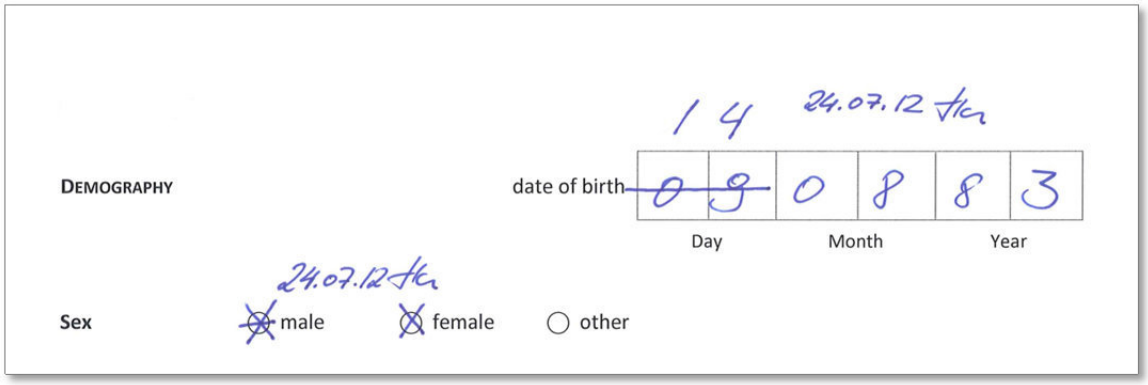
Name: _____

Signature: _____

Stamp:

Register: 6 Months

Instructions for completing Case Report Form



E·S·P·O·I·R

Center | Patient N°

Physical Examination			Page 1/2
	◯ Discharge	◯ 3 | ◯ 6 | ◯ 12 | ◯ Months	

Physical Examination Date of visit (Day / Month / Year)

Height ___ cm Weight ___ kg

Heart rate (resting) ___ beats/min

Blood pressure ___ (systolic) / ___ (diastolic) mmHg

NYHA Classification ◯ I ◯ II ◯ III ◯ IV ◯ unknown

Medication ◯ none ◯ platelet inhibitors ◯ Warfarin ◯ ß-Blockers ◯ others *(please specify)*

Clinical signs of haemolysis available at current visit ◯ none ◯ yes *(please specify ↙)*

	Unit	other Unit *(please specify)*	Value	Evaluation normal	Evaluation abnormal
white blood cells	10^3/µl			◯	◯
free hemoglobin (plasma)	g/dl			◯	◯
haptoglobin	g/l			◯	◯
CRP	mg/l			◯	◯
LDH	U/l			◯	◯

Clinical signs of arrhythmia available at current visit ◯ none ◯ others *(please specify below)*

ventricular extrasystolia ◯ mild ◯ moderate ◯ severe

Additional information:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

Center Patient N°

Physical Examination			Page 2/2
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Adverse Reaction ◯ no

◯ yes *(please specify below;*
if more than one adverse reaction: please add additional pages)

related to ESPOIR PV ◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved ◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention *(Annex A)*

Additional information concerning adverse reaction:

[Date]	*[Name]*	*[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·O·I·R

Center | Patient N°

Echocardiography

Page 1/2

◯ Baseline ◯ Discharge ◯ 3 | ◯ 6 | ◯ 12 | ◯ Months

◯ **no echocardiography has been performed**

Date of examination: Day / Month / Year

Right atrial dilatation ◯ yes ◯ no

Left atrial dilatation ◯ yes ◯ no

Tricuspid regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Mitral regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Right ventricle
diameter end-diastolic mm
diameter end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Left ventricle
end-diastolic mm
end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Pulmonary valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

Aortic valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

E·S·P·O·I·R

Center | Patient N°

Echocardiography			Page 2/2
◯ **Baseline**	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Pulmonary regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Aortic regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Calcification ◯ yes ◯ no

Calcification ◯ yes ◯ no

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Right ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Right pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Remarks

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

corlife oHG
CRF Espoir
Feodor-Lynen-Str. 23

D-30625 Hannover
Allemagne/Germany

Short Message

○ CRF
○ DVD
○ Other: _____

_____

Date: _____

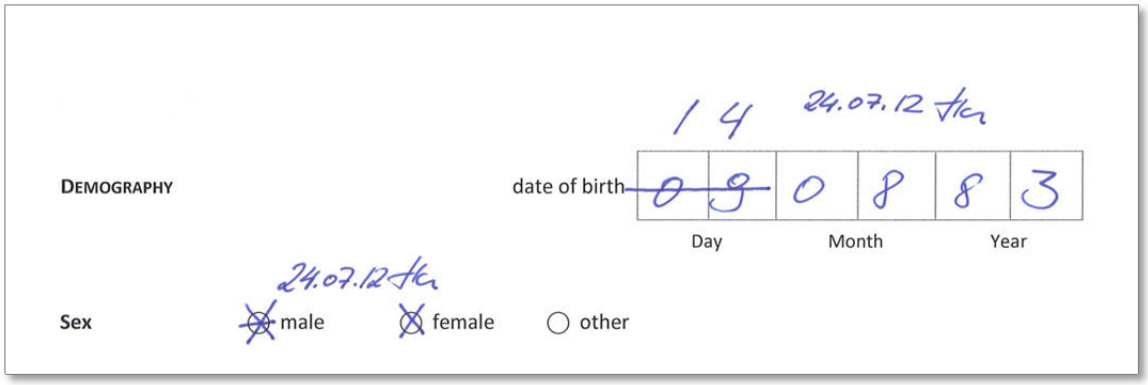
Name: _____

Signature: _____

Stamp:

Register: 12 Months

Instructions for completing Case Report Form



E·S·P·O·I·R

Center | Patient N°

Physical Examination			Page 1/2
	◯ Discharge	◯ 3 | ◯ 6 | ◯ 12 | ◯ Months	

Physical Examination Date of visit (Day / Month / Year)

Height ___ cm Weight ___ kg

Heart rate (resting) ___ beats/min

Blood pressure ___ (systolic) / ___ (diastolic) mmHg

NYHA Classification ◯ I ◯ II ◯ III ◯ IV ◯ unknown

Medication ◯ none ◯ platelet inhibitors ◯ Warfarin ◯ ß-Blockers ◯ others *(please specify)*

Clinical signs of haemolysis available at current visit ◯ none ◯ yes *(please specify ↙)*

	Unit	other Unit *(please specify)*	Value	Evaluation normal	Evaluation abnormal
white blood cells	10^3/µl			◯	◯
free hemoglobin (plasma)	g/dl			◯	◯
haptoglobin	g/l			◯	◯
CRP	mg/l			◯	◯
LDH	U/l			◯	◯

Clinical signs of arrhythmia available at current visit ◯ none ◯ others *(please specify below)*

ventricular extrasystolia ◯ mild ◯ moderate ◯ severe

Additional information:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

Center Patient N°

Physical Examination			Page 2/2
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Adverse Reaction ◯ no

◯ yes *(please specify below;*
if more than one adverse reaction: please add additional pages)

related to ESPOIR PV ◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved ◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention *(Annex A)*

Additional information concerning adverse reaction:

[Date]	*[Name]*	*[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·O·I·R

Center | Patient N°

Echocardiography

Page 1/2

◯ Baseline ◯ Discharge ◯ 3 | ◯ 6 | ◯ 12 | ◯ Months

◯ **no echocardiography has been performed**

Date of examination: Day / Month / Year

Right atrial dilatation ◯ yes ◯ no

Left atrial dilatation ◯ yes ◯ no

Tricuspid regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Mitral regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Right ventricle
diameter end-diastolic mm
diameter end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Left ventricle
end-diastolic mm
end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Pulmonary valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

Aortic valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

E·S·P·O·I·R

Center | Patient N°

Echocardiography			Page 2/2
◯ **Baseline**	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Pulmonary regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Aortic regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Calcification ◯ yes ◯ no

Calcification ◯ yes ◯ no

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Right ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Right pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Remarks

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

Center Patient N°

MRI			Page 1/1
◯ **Baseline**	◯ **12 months follow-up**	◯ **other:**	

◯ **there was no MRI performed**

Date of MRI examination

Day Month Year

[Date]	*[Name]*	*[Signature]*

	Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.	white, blue: corlife; yellow: study center
		Version 10/2013

E·S·P·O·I·R

Center | Patient N°

MRI			Page 1/1
◯ Baseline	◯ 12 months follow-up	◯ other:	

date of MRI examination as indicated on disc: Day | Month | Year

Right ventricular volume

end-diastolic . ml/m²

end-systolic . ml/m²

Left ventricular volume

end-diastolic . ml/m²

end-systolic . ml/m²

Right ventricular mass

. g/m²

Left ventricular mass

. g/m²

Pulmonary artery flow

max. velocity . m/s

regurgitation . %

Aorta ascendens flow

max. velocity . m/s

regurgitation . %

Pulmonary valve diameter mm

proximal stenosis ◯ yes ◯ no

distal stenosis ◯ yes ◯ no

valvular stenosis ◯ yes ◯ no

Aortic valve diameter mm

proximal stenosis ◯ yes ◯ no

distal stenosis ◯ yes ◯ no

valvular stenosis ◯ yes ◯ no

Remarks:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, yellow: corlife; yellow: blue center

Version 10/2013

E·S·P·  ·I·R

corlife oHG
CRF Espoir
Feodor-Lynen-Str. 23

D-30625 Hannover
Allemagne/Germany

Short Message

○ CRF
○ DVD
○ Other: _____

_____

Date: _____

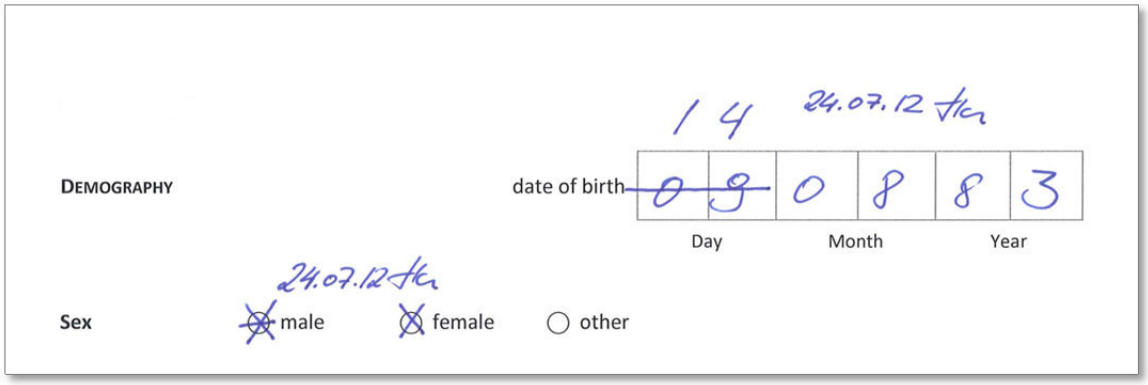
Name: _____

Signature: _____

Stamp:

Register: other

Instructions for completing Case Report Form



E·S·P·O·I·R

Center | Patient N°

Physical Examination			Page 1/2
	◯ Discharge	◯ 3 | ◯ 6 | ◯ 12 | ◯ Months	

Physical Examination Date of visit (Day / Month / Year)

Height ___ cm Weight ___ kg

Heart rate (resting) ___ beats/min

Blood pressure ___ (systolic) / ___ (diastolic) mmHg

NYHA Classification ◯ I ◯ II ◯ III ◯ IV ◯ unknown

Medication ◯ none ◯ platelet inhibitors ◯ Warfarin ◯ ß-Blockers ◯ others *(please specify)*

Clinical signs of haemolysis available at current visit ◯ none ◯ yes *(please specify ↙)*

	Unit	other Unit *(please specify)*	Value	Evaluation normal	Evaluation abnormal
white blood cells	10^3/µl			◯	◯
free hemoglobin (plasma)	g/dl			◯	◯
haptoglobin	g/l			◯	◯
CRP	mg/l			◯	◯
LDH	U/l			◯	◯

Clinical signs of arrhythmia available at current visit ◯ none ◯ others *(please specify below)*

ventricular extrasystolia ◯ mild ◯ moderate ◯ severe

Additional information:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

Center Patient N°

Physical Examination			Page 2/2
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Adverse Reaction ◯ no

◯ yes *(please specify below;*
if more than one adverse reaction: please add additional pages)

related to ESPOIR PV ◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved ◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention *(Annex A)*

Additional information concerning adverse reaction:

[Date]	*[Name]*	*[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·O·I·R

Center | Patient N°

Echocardiography

Page 1/2

◯ Baseline ◯ Discharge ◯ 3 | ◯ 6 | ◯ 12 | ◯ Months

◯ **no echocardiography has been performed**

Date of examination: Day / Month / Year

Right atrial dilatation ◯ yes ◯ no

Left atrial dilatation ◯ yes ◯ no

Tricuspid regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Mitral regurgitation
◯ mild
◯ moderate
◯ severe
max. velocity . m/sec

Right ventricle
diameter end-diastolic mm
diameter end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Left ventricle
end-diastolic mm
end systolic mm
function ◯ normal ◯ mildly reduced ◯ severely reduced

Pulmonary valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

Aortic valve
diameter mm

PW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

CW-Doppler
velocity . m/sec
mean gradient mmHg
max. gradient mmHg

E·S·P·O·I·R

Center | Patient N°

Echocardiography			Page 2/2
◯ **Baseline**	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

Pulmonary regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Aortic regurgitation

◯ none ◯ trace ◯ mild
◯ mild-moderate ◯ moderate
◯ moderate-severe ◯ severe

Calcification ◯ yes ◯ no

Calcification ◯ yes ◯ no

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Leaflets

normal mobility ◯ yes ◯ no
thickness [ ] . [ ] mm

Right ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left ventricular outflow *(optional)*

PW-Doppler
velocity [ ] . [ ] m/sec
mean gradient [ ][ ] mmHg
max. gradient [ ][ ] mmHg

Left pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Right pulmonary artery *(optional)*

velocity [ ] . [ ] m/sec

Remarks

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

Center Patient N°

MRI			Page 1/1
◯ **Baseline**	◯ **12 months follow-up**	◯ **other:**	

◯ **there was no MRI performed**

Date of MRI examination

Day Month Year

[Date]	*[Name]*	*[Signature]*

	Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.	white, blue: corlife; yellow: study center
		Version 10/2013

E·S·P·O·I·R

Center | Patient N°

MRI			Page 1/1
◯ Baseline	◯ 12 months follow-up	◯ other:	

date of MRI examination as indicated on disc: Day | Month | Year

Right ventricular volume

end-diastolic . ml/m²

end-systolic . ml/m²

Left ventricular volume

end-diastolic . ml/m²

end-systolic . ml/m²

Right ventricular mass

. g/m²

Left ventricular mass

. g/m²

Pulmonary artery flow

max. velocity . m/s

regurgitation . %

Aorta ascendens flow

max. velocity . m/s

regurgitation . %

Pulmonary valve diameter mm

proximal stenosis ◯ yes ◯ no

distal stenosis ◯ yes ◯ no

valvular stenosis ◯ yes ◯ no

Aortic valve diameter mm

proximal stenosis ◯ yes ◯ no

distal stenosis ◯ yes ◯ no

valvular stenosis ◯ yes ◯ no

Remarks:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, yellow: corlife; yellow: blue center

Version 10/2013

E·S·P·  ·I·R

corlife oHG
CRF Espoir
Feodor-Lynen-Str. 23

D-30625 Hannover
Allemagne/Germany

Short Message

○ CRF
○ DVD
○ Other: _____

_____

Date: _____

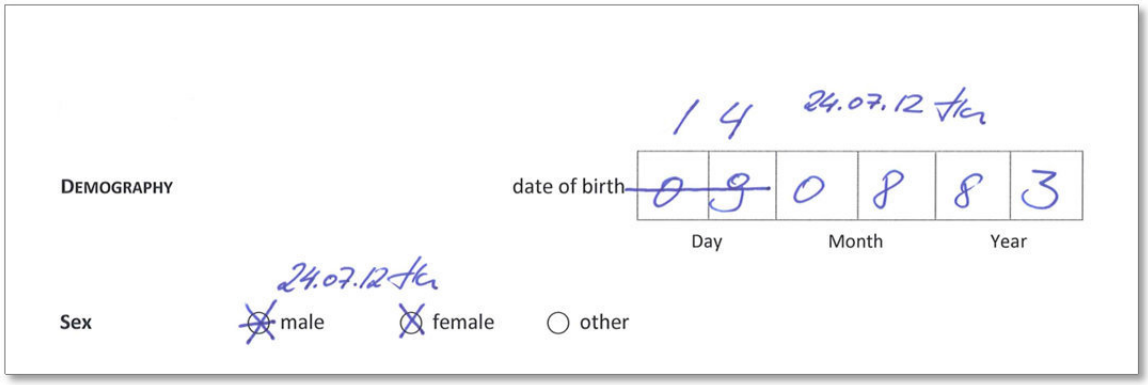
Name: _____

Signature: _____

Stamp:

Register: Re-Intervention / AR

Instructions for completing Case Report Form



E·S·P·  ·I·R

Center		Patient N°		

Re-Operation or Catheter Intervention

RE-OPERATION date of re-operation: | | | | | | | (day / month / year)

Type of re-operation

- ◯ explantation of ESPOIR PV / implantation of new valve
- ◯ patch plasty
- ◯ other *(please specify)*

Reason for re-operation

- ◯ stenosis ◯ regurgitation ◯ endocarditis
- ◯ other *(please specify)*

CATHETER BASED INTERVENTION ON IMPLANTED *ESPOIR PV*

date of intervention: | | | | | | | (day / month / year)

Type of intervention

- ◯ balloon dilatation ◯ percutaneous valve implantation
- ◯ other *(please specify)*

Reason for intervention

- ◯ stenosis ◯ regurgitation ◯ endocarditis
- ◯ other *(please specify)*

Remarks

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·  ·I·R

Center		Patient N°		

Re-Operation or Catheter Intervention

RE-OPERATION date of re-operation: | | | | | | | (day / month / year)

Type of re-operation

- ◯ explantation of ESPOIR PV / implantation of new valve
- ◯ patch plasty
- ◯ other *(please specify)*

Reason for re-operation

- ◯ stenosis ◯ regurgitation ◯ endocarditis
- ◯ other *(please specify)*

CATHETER BASED INTERVENTION ON IMPLANTED *ESPOIR PV*

date of intervention: | | | | | | | (day / month / year)

Type of intervention

- ◯ balloon dilatation ◯ percutaneous valve implantation
- ◯ other *(please specify)*

Reason for intervention

- ◯ stenosis ◯ regurgitation ◯ endocarditis
- ◯ other *(please specify)*

Remarks

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·◯·I·R

Center Patient N°

Adverse Reaction			Page 1/1
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

related to ESPOIR PV

◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved

◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention

Additional information concerning adverse reaction:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·◯·I·R

Center Patient N°

Adverse Reaction			Page 1/1
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

related to ESPOIR PV

◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved

◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention

Additional information concerning adverse reaction:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·◯·I·R

Center Patient N°

Adverse Reaction			Page 1/1
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

related to ESPOIR PV

◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved

◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention

Additional information concerning adverse reaction:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·◯·I·R

Center Patient N°

Adverse Reaction			Page 1/1
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

related to ESPOIR PV

◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved

◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention

Additional information concerning adverse reaction:

[Date] *[Name]* *[Signature]*

Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

E·S·P·◯·I·R

Center Patient N°

Adverse Reaction			Page 1/1
	◯ **Discharge**	◯ **3** | ◯ **6** | ◯ **12** | ◯ **Months**	

related to ESPOIR PV

◯ no

◯ yes *(please specify)* ◯ unknown *(please specify)*

(a) grade: ◯ mild ◯ moderate

treatment: ◯ no ◯ medication *(please specify below)*

outcome: ◯ resolved ◯ unresolved

◯ resolved with sequelae

(b) ◯ ***Serious Adverse Reaction***
(Form delivered with implant)

(c) ◯ re-operation / catheter based intervention

Additional information concerning adverse reaction:

[Date] *[Name]* *[Signature]*

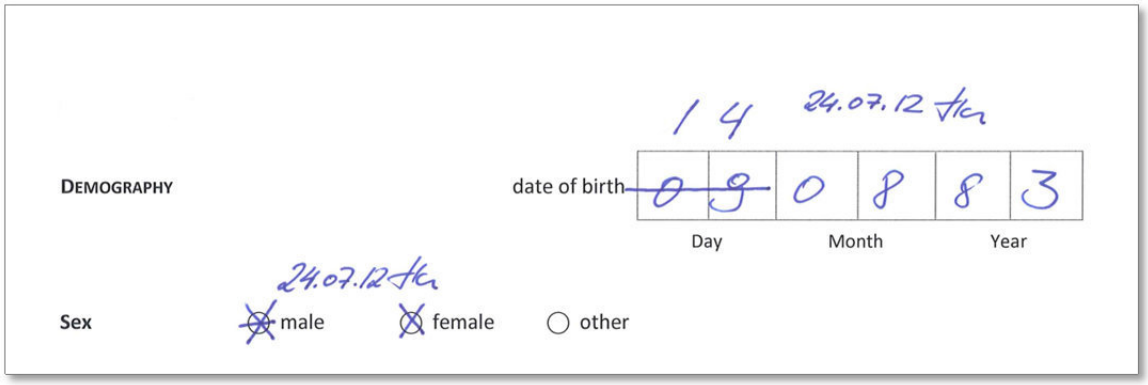
Please do not collect more data than required for the medical treatment of your patient with ESPOIR PV. All data is collected within the treating physician's sole and reasonable discretion.

white, blue: corlife; yellow: study center

Version 10/2013

Schreibschutz

Instructions for completing Case Report Form



APPENDIX 07

Product Liability Insurance

CHUBB INSURANCE COMPANY OF EUROPE SE
Fleethof-Stadthausbrücke 1-3 20355 Hamburg
Telefon: +49-(0)40-369805-0 · Fax: +49-(0)40-369805-390
www.chubb.com/germany

Certificate of Insurance	
Policy Number	35996646

Policy Holder	Insurer
corlife oHG Feodor-Lynen-Str. 23 30625 Hannover	Chubb Insurance Company of Europe SE Fleethof-Stadthausbrücke 1-3 20355 Hamburg

Period of Insurance	from 1-Dec-2013 to 1-Dec-2014 This insurance policy is automatically renewed for a further period of insurance unless it is cancelled three months prior to the expiry date of the current period.
Scope of Coverage	General Liability including products and completed operations Within the scope defined by the terms and conditions of this insurance our company grants the insured coverage against third-party-claims on the basis of legal liability provisions under private law with respect to any bodily injury and property damage occurring during validity of the insurance. This policy insures bodily injury and property damage occurring world-wide, excluding occurrences in USA/Canada / resulting from direct exports or operations performed in these territories. The coverage extends to bodily injury and property damage caused by products manufactured or supplied and work or other services performed by the insured. This cover commences at the time the policyholder markets the products, completes the work or has performed the services (Product completed operations liability).
Policy Limit	€ 5.000.000,00 each and every occurrence for bodily injury and property damage aggregated once per year. This certificate of insurance neither affirmatively nor negatively amends, extends or alters the coverage afforded by any insurance described herein and is only declarative and confers no rights upon the certificate holder. The policy 35996646 only is legally binding. This certificate does not amend, extend or alter the coverage.

Chubb Insurance Company of Europe SE 17. Januar 2014

Appendix 08 - Local Investigators

1. Germany

   Medizinische Hochschule Hannover (MHH)

   Dep. for Cardiothoracic, Transplantation & Vascular Surgery

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2. Republic of Moldova

   Universitatea de Stat de Medicina si Farmacie „Nicolae Testemitanu“(SMPHU)

   Prof. Dr. Anatol Ciubotaru

   Dr. Oleg Repin

   Dr. Oxana Maliga

3. The Netherlands

   Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum (LUMC)

   Congenital Cardiothoracic Surgery

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   Dr. Eline Bruggemans, E.F.Bruggemans@lumc.nl

4. United Kingdom

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5. Italy

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   Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari
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   Azienda Ospedaliera di Padova (AOP)
   U.O.C. di Cardiochirurgia Pediatrica e Cardiopatie Congenite
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6. France

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7. Switzerland

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8. Belgium

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