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Abstract (for dissemination)	EurValve will develop and deploy a clinically-compliant Decision Support System (DSS) for Aortic Stenosis and Mitral regurgitation. For formal testing and evaluation of the developed DSS a clinical study will be conducted. This document describes the clinical study cohort and patient inclusion criteria and outlines the study's design.
Keywords	Aortic Stenosis, Mitral Regurgitation, Decision Support, Digital Patient, Predictive Modelling, Simulation

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23- May -2016	0v2	Alexander Meyer	add ethics section
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31-May-16	1v1	PMO	Minor corrections
31-May-16	1v2	Pat Lawford/PMO	Minor corrections

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

EXECUTIVE SUMMARY

AIM

EurValve will develop and deploy a clinically-compliant Decision Support System (DSS) for Aortic Stenosis and Mitral Regurgitation. For formal testing and evaluation of the developed DSS, a clinical study will be conducted. This document describes the clinical study cohort and outlines the study's design.

RESULTS

A clinical prospective multi-centre cohort study with 120 patients enrolled in two groups is planned:

- Group 1: Aortic valve disease (N=60, per clinical centre N=20)
- Group 2: Mitral valve disease (N=60, per clinical centre N=20)

This first step of model evaluation is observational research taking place in a routine clinical context and therefore the choice of treatment depends solely upon the clinician's choice. The data will be gathered at three visits: before intervention (surgery or TAVI, at the time of intervention and after the intervention.

Inclusion criteria are chosen according to the ESC/EACTS guidelines. Exclusion criteria have been chosen to ensure that a complete data set is collected for each patient.

By July 2016 all clinical centres are expected to have submitted the necessary information required to seek an ethical opinion.

CONCLUSIONS

The cohort defined herein has been chosen to represent the vast majority of patients diagnosed with one of the two most prevalent valvular heart diseases, whilst ensuring completeness of follow up. This cohort definition is a solid basis for the first step of the evaluation of the novel DSS that will be developed within the EurValve project.

1 INTRODUCTION AND OBJECTIVES

Within the EU, the management of heart valve disease patients is carried out with reference to the recommendations of the Guidelines on the Management of Valvular Heart disease, an output of a Joint Task Force from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)[1]. A clinical member of the EurValve Consortium (Dr Falk, DHZB) was involved in the formalisation of these guidelines.

Current guidelines conclude that improved scoring systems for predicting risks and outcomes of valve surgery and catheter based procedures are highly desirable; at present, the medical decision is limited to the assessment of clinical symptoms, arterial blood pressures and global pump function (ejection fraction and ventricular chamber size). By their nature, such gross parameters yield a large range of thresholds and are subject to high inter-individual variability; consequently, they do not reflect the complete pathophysiological state for a given patient.

EurValve will develop and deploy a clinically-compliant Decision Support System (DSS) for the management of the two most prevalent Valvular Heart Diseases; Aortic Stenosis and Mitral regurgitation (Figure 1). After initial testing and evaluation of the DSS with retrospective data, a prospective clinical multi-centre study will be conducted to enable formal evaluation of the sensitivity of the DSS output to the variation and uncertainty of model inputs and to facilitate comparison between current clinical decision-making and the outputs of the DSS.

This document describes the clinical study cohort and outlines the study design.

[1] Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC)1; European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012 Oct;33(19):2451-96. doi: 10.1093/eurheartj/ehs109. Epub 2012 Aug 24.

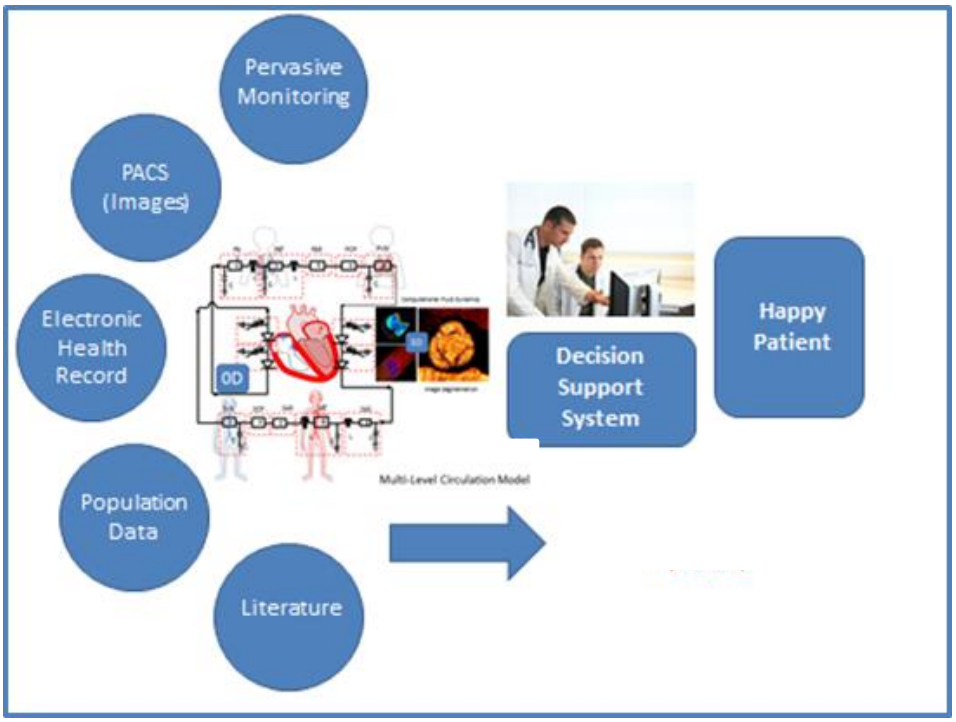

Figure 1: Model-based interpretation of heterogeneous data to provide decision support

2 STUDY DESIGN

The EurValve project will implement, test and evaluate a DSS for aortic valve replacement and mitral valve replacement/repair. Testing and evaluation will be carried out within a prospective clinical multi-centre study, the overall design of which is shown in Figure 2.

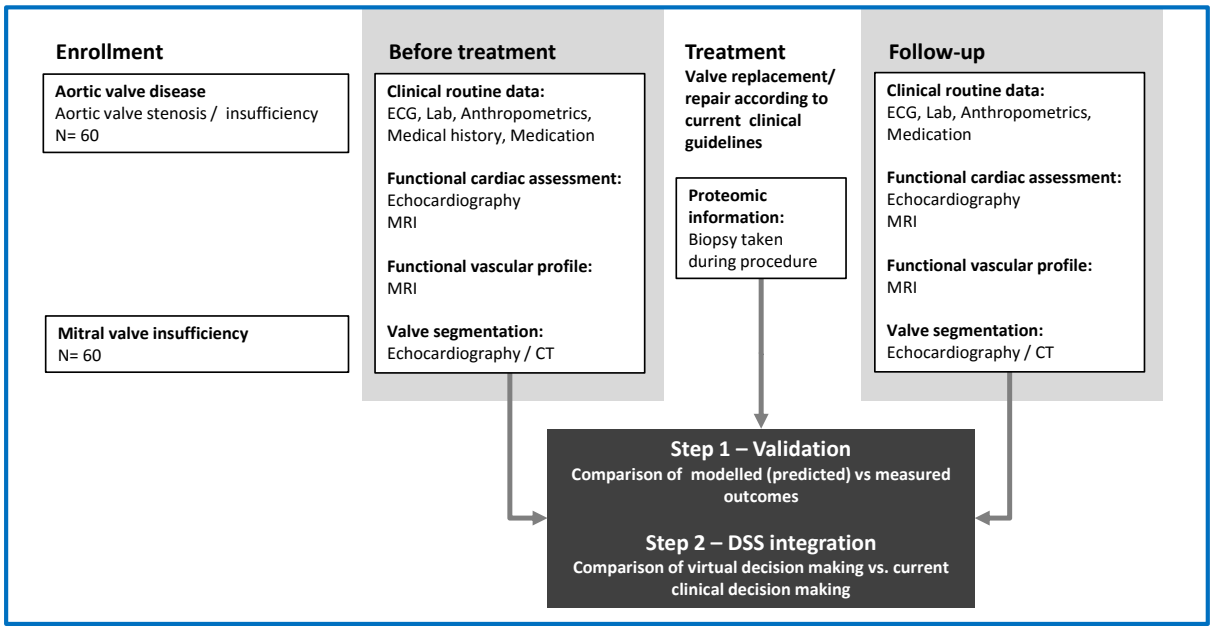

Figure 2 Prospective clinical study design

2.1 Study Population

Participating clinical centres will enrol 120 patients from within two subgroups:

- Group 1: patients with aortic valve disease (aortic valve stenosis / regurgitation)
  - Overall N = 60
  - per clinical centre N = 20
- Group 2: patients with mitral valve disease (mitral regurgitation)
  - Overall N = 60
  - per clinical centre N = 20

It has been calculated that 60 patients per group are sufficient to achieve a power of greater than 80% to detect a true difference of greater than 25 % in the DSS result in comparison to the actual result. The equal sample-size split among centres is an initial pragmatic setting. If significant differences in enrolment are observed, an adjustment to the sample splitting proportion will be made.

Sheffield Teaching Hospitals NHS Foundation Trust and the German Heart Institute, Berlin will enrol patients planned for surgical aortic valve replacement (SAVR) and mitral valve repair/replacement (MVR). At the Catharina Hospital, in addition to SAVR and MVR patients, those planned for transcatheter aortic valve implantation (TAVI) will also be enrolled.

2.1.1 Inclusion Criteria

Inclusion criteria are backed by the current European guidelines on the management of valvular heart disease[2]. Behind each defined criterion the class of recommendation and the level of evidence are given as graded by the guideline committee (see Figure 3 and Figure 4).

[2] Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC)1; European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012 Oct;33(19):2451-96. doi: 10.1093/eurheartj/ehs109. Epub 2012 Aug 24.

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Figure 3: Recommendation classes, from ESC/EACTS joint guidelines on VHD

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

Figure 4: Levels of evidence, from ESC/EACTS joint guidelines on VHD

- The patient must give Informed Consent before being enrolled in the study.
- Only elective cases will be eligible for inclusion.
- For mitral disease, patients will be recruited with;
  - Severe degenerative or functional mitral regurgitation with the need for MVR according to the ESC/EACTS guidelines.
    - *Degenerative mitral regurgitation*
      - Symptomatic patients with LVEF >30% and LVESD < 55mm (I B)
      - Asymptomatic patients with LV dysfunction (LVESD ≥45 mm and/or LVEF ≤60% (I C)
      - Asymptomatic patients with LVEF > 50%, new onset of atrial fibrillation or pulmonary hypertension (systolic pulmonary pressure at rest >50 mmHg) (IIa C)
      - Patients with severe LV dysfunction (LVEF < 30% and LVESD > 55 mm) refractory to medical therapy with high likelihood of durable repair and low comorbidity. (IIa C)
    - *Functional mitral regurgitation*
      - Patients with severe MR (EROA >= 20 mm², Regurgitation volume > 30 ml) undergoing CABG, and LVEF >30% (I C)
      - Patients with moderate MR undergoing CABG (IIa C)
      - Symptomatic patients with severe MR, LVEF < 30 %, option for revascularisation, and evidence of viability (IIa C)
- For aortic valve disease, patients will be recruited with;
  - Severe acquired degenerative aortic valve disease with the need for SAVR or TAVI according to the ESC/EACTS guidelines
    - *Severe Aortic stenosis*
      - Symptomatic patients (I B)
      - Patients undergoing CABG or surgery of ascending aorta or another valve (I C)
      - Asymptomatic patients with abnormal exercise test (I C) / LVEF < 50% (I C) / blood pressure drop on exercise / peak gradient > 5.5 m/sec ((IIa C)
      - Symptomatic patients with low flow, low gradient (< 40mmHg) and normal LVEF (IIa C)
      - Asymptomatic patients with low flow, low gradient (< 40mmHg) and reduced LVEF with evidence for flow reserve (IIa C)

2.1.2 Exclusion Criteria

The following exclusion criteria have been chosen to maximise the likelihood of obtaining a valid DSS and to minimise the likelihood of patients being lost to follow up. For these reasons, rare causes and emergency indication of aortic stenosis and mitral regurgitation are excluded, as these mostly represent separate entities with grossly different clinical managements and outcomes.

- Age < 18
- Inability or unwillingness to give formal consent.
- Emergency interventions
- Active infective valvular disease or evidence of valvular damage by recent endocarditis
- Valvular malfunction directly associated with aortic root disease
- Mitral regurgitation combined with moderate or severe mitral stenosis
- Mitral stenosis
- Aortic regurgitation as the leading aortic valve pathology
- Inability or unwillingness to complete follow up (Visit 2 – see 2.4 below)
- MRI contraindications
    - Implanted pacemaker
    - Metallic foreign body
    - Severe claustrophobia
- CT contraindications
    - Known iodine or contrast agent allergy
    - Hyperhidrosis
    - Pregnancy

2.2 Enrolment of participants

Enrolment will take place in the patient's routine clinical setting. Patients will be screened upon admission. Following a positive screening result, informed consent will be obtained.

2.3 Visits

The study will have the following visits at all clinical centres:

- **Visit 1**: All patients will be investigated before valve intervention by MRI and/or CT imaging, ECG, laboratory tests and anthropometric measurement (blood pressure, body weight, clinical status etc.). CT and echo examinations will be carried out according to the specific hospital's standard pre-operative examination protocols. MRI examinations will be carried out according to the protocol shown in Annex 4.1 All acquired data will be used for the digital patient and consecutive modelling.

- **Intervention**: At the time of intervention (valve replacement/repair or TAVI). In EurValve all patients will be treated according to current clinical guidelines. At the Berlin clinical centre an additional myocardial biopsy will also be performed in patients undergoing surgery, with the biomaterial being used for proteomic analysis.

- **Visit 2**: Patients will be followed-up after treatment, undergoing the full study protocol once again. This will facilitate comparison between the modelled (predicted) and measured outcome data. After this validation step, a randomised controlled experiment will be designed as part of WP Task 6.4 in order to assess the efficiency of a DSS. In this second step, a comparison between virtual decision making using a DSS and the current clinical decision-making process will be carried out.

2.4 Data collection

In this study data will be collected for use in development and validation. These data will be collected in accordance with the data definition provided in deliverable D4.1. More specifically, data will be collected as described in Tables 1 to 9 of D4.1, to record meta-data as well as data on demographics, medications, risk factors, diagnoses, physiological and laboratory measurements, echocardiographic measurements, MRI, CT measurements, and operative data. See D4.1 for lists of data fields. Note, as mentioned in D4.1, that the precise lists of data fields described in D4.1 are not yet final and may undergo adaptations and additions in the coming period.

To ensure a proper data foundation testing and validation the DSS, obtaining a complete dataset for each patient will be a priority.

2.5 Ethics

As a clinical prospective cohort study, the DSS validation must undergo ethical review by regulatory committees and/or local institutional review boards. The German Heart Institute Berlin made a submission on 13 May 2016 (see Annex 4.2); a favourable opinion is expected before June 2016.

Sheffield Teaching Hospitals NHS Foundation Trust and the Catharina Hospital are expected to submit similar applications by July 2016.

3 List of Abbreviations

AI	Aortic insufficiency
AR	Aortic regurgitation
AS	Aortic stenosis
AoV	Aortic Valve
BSA	Body surface area
CABG	Coronary artery bypass grafting
CT	Computer Tomography
CW	Continuous wave
DHZB	Deutsches Herzzentrum Berlin (German Heart Institute Berlin)
DSS	Decision Support System
EACTS	European Association for Cardio-Thoracic-Surgery
ECG	Electrocardiogram
eCRF	Electronic case report forms
ED	End diastole
EF	Ejection fraction
EROA	Effective regurgitant orifice area
ES	End systole
ESC	European Society of Cardiology
LV	Left ventricle
LVESD	Left ventricle end systolic diameter
LVOT	Left ventricular outflow tract
MR	Mitral regurgitation
MR(I)	Magnetic Resonance (Imaging)
MVR	Mitral valve repair/replacement
PW	Pulse-wave
SAVR	Surgical aortic valve replacement
TAVI	Transcatheter aortic valve implantation
WP	Workpackage

4 ANNEX

4.1 MRI scan protocol

The MRI protocol will be used across all clinical sites to ensure consistency in the acquisition of functional parameters. Sequences are clinical routine sequences unless marked otherwise. An optional T1 Mapping will be performed wherever possible to allow an additional assessment of myocardial fibrosis.

Table 1 MRI examination protocol

	MRI Scan Protocol
	Weight _____ Height _____
1.	Survey
2.	Planning sequences CINE pseudo 2 chamber CINE pseudo 4 chamber CINE aortic arch
3.	CINE short axis (only ventricle and valve region)
4.	CINE 4 chamber CINE 2 chamber left CINE 3 chamber left
5.	CINE aortic valve (orthogonal 3 Slices 8 mm)
6.	CINE ascending aorta cross section (at level of pulmonary artery bifurcation)
7.	CINE descending aorta cross section (at level of pulmonary artery bifurcation)
	BLOOD PRESSURE right arm: SYS_____ DIA_____ Heart rate _____
8.	2D Q-flow: just distal to the aortic valve, also including descending aorta (if not possible separate sequence)
9.	2D Q-flow: covering mitral valve inflow with LVOT outflow temporal resolution 70 phases/heart cycle
10.	After intervention: Black blood sequence: orthogonal stack covering the area before the valve until mid of ascending aorta
11.	T1 Mapping native** Molli (short axis mid & basal)
12.	GRID- Tagging: ** 1) Short axis (3 slices): apical, mid, basal 2) 2 chamber 3) 4 chamber
13.	4D Flow: covering LVOT and ascending aorta (velocity encoding 100 cm/s above Vmax from echocardiography)
	Contrast injection: Dotarem (0.2 mmol/kg *)**
14.	3D stack covering whole heart and aorta (enddiastolic)
	>8 Min after contrast
15.	Look-Looker* ** Late Gadolinium enhancement (2 mid / basal short axis)* ** 3D Scar sequence* **
	15-20 Min after contrast
16.	T1 Mapping* ** Molli after contrast agent (SAX mid & basal)
17.	4D Flow covering left ventricle and left atrium (velocity encoding 80 cm/s)

* In patients with renal function > 60ml/min/1,73m^2 and signed consent for contrast study
** Optional sequences

4.2 Echocardiography

An echocardiographic protocol was defined representing the transthoracic standard in the assessment of the aortic/mitral valve. In most patients an additional intra-operative echocardiographic procedure will be performed to capture the relevant valve geometries in a 3D sequence.

- **Parasternal long axis view**
  - 2 D cine look
  - M-Mode of LV
  - Diameter of LVOT
- **Apical 4-chamber view**
  - 2D (obtaining the longest and widest LV cavity, endocardium, exclude papillary musc)
  - atrium endsystolc for volumetry
  - TAPSE
  - MAPSE
  - Colour MR
  - PW MV velocity
  - CW for evaluation of MR
  - Doppler tissue imaging myocardial velocity mitral annulus (Inter-ventricular septum, lateral wall, right ventricular free wall at the tricuspid annular level) freeze spectral (50-75 mm/s display, at least 3 beats).
- **Apical 5-chamber view**
  - PW of the LVOT
  - CW of the aortic valve
  - Colour for evaluation of AI (4 beats)
  - Diameter

4.3 CT scan protocol

The preferred CT scan parameters were defined as shown below. These will be adapted to the individual scanners at all 3 clinical sites.

AVR/MKR Computed Tomography

DHZB: Preferred Examination Protocol

Scanner	SOMATOM Definition Flash
Scan mode	Flash mode
ECG gating	Yes
Tube voltage	80 KV
Tube current	256 ref. mAs,
Dose modulation	CARE Dose4D, CARE kV
Rotation time	0.28 sec
Pitch	3.0
Slice collimation	128 x 0.6 mm
Slice width	0.6 mm
Reconstruction increment	0.6 mm
Reconstruction kernel	……..
Scan length	Thorax+Abdomen
DLP	320 mGy*cm
Effective dose	3-4 mSv
Contrast	Imeron 400
Volume	1.0 ml/kg or less
Flow rate	4 ml/s
Start delay	Bolus tracking (descending aorta)

4.4 Ethical Submission German Heart Institute Berlin

All clinical sites will submit an ethical proposal to their local ethical committees. At DHZB the proposal was received by the committee on 05-May-2016 (document shown below). The project was successfully presented on 26-May-2016 without any relevant objections. DHZB is currently awaiting the formal approval of the study in order to begin the recruitment process.

CHARITÉ

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17.05.16

EURValve – Modellbasierte Simulation eines Herzklappenersatzes und dessen Auswirkung auf den Herzmuskel
Antragsnummer: EA2/093/16
Vorgang vom 13.05.16, Eingang am 17.05.16

Sehr geehrter Herr Professor Kühne,

hiermit bestätigen wir Ihnen den Eingang Ihres Schreibens mit folgenden Anlagen:

- Dateien per E-Mail am 13.05.16
- Ethikantrag, 13.05.16
- Patienteninformation, Version vom 13.05.2016
- Einwilligungserklärung, Version vom 13.05.2016
- Leseexemplare für die Mitglieder

Es fehlt:

- Beiliegend erhalten Sie einen Gebührenbescheid. Bitte übersenden Sie einen Überweisungsbeleg mit der o.g. EA-Nr. an Ethikkommission@charite.de

Die Studie wird dem Ethikausschuss am Campus Charité Virchow übertragen und erhält die o.g. Antragsnummer, **welche bitte bei jedwedem Schriftwechsel bezüglich o.g. Studie anzugeben ist.**
Die Studie wird am 26.05.16 beraten. Sie erhalten eine Einladung 1 Woche vor der Sitzung.

Wir erheben gem. § 2 Abs. 2 der Gebührensatzung der Ethikkommission der Charité (Amtl. Mitteilungsblatt der Charité vom 27.08.07) für die Bearbeitung der o.g. Studie durch die Ethikkommission eine Gebühr in Höhe von **200,- Euro.**

Mit freundlichen Grüßen

Dr. med. K. Orzechowski
Med. Geschäftsführerin