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Abstract (for dissemination)	The EurValve project will combine multiple complex modelling components developed in recent EC-funded research projects to develop a comprehensive, clinically-compliant decision-support system (DSS) that will assist clinicians with the complex task of optimising intervention in the dominant two conditions within Valvular Heart Disease, namely Aortic Stenosis and Mitral Regurgitation. This document presents the specification for the DSS itself, outlining the content, appearance and operation of the anticipated system.
Keywords	Decision Support, Valvular Heart Disease, Aortic Stenosis, Mitral Regurgitation

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EXECUTIVE SUMMARY

SCOPE

EurValve will develop a clinically-compliant Decision Support System to support healthcare professionals in the management of Valvular Heart Disease. The system will be designed also to assist the clinician in communication with the patient, enabling the easy description of the consequences of the disease, the prognosis, and the treatment options. It will be implemented as a plug-in within the framework of the EndoSize® software, a commercially available CE-marked and FDA-approved modular platform that addressed the specific planning needs of endovascular and endovalvular procedures. Specifically, it will operate on a stand-alone workstation and will be integrated into the already available planning workflow which currently includes a geometrical data extraction process, a standardised keypoint-based measurement process, and a procedure strategy process based on warnings relating to the indications for use of implant devices.

OBJECTIVES

The concepts and measures that will drive the DSS are highly heterogeneous, including such diverse elements as the parameters in the electric analogue circulation model, the pressure and flow distributions, demographic data, proteomic data, image data, co-morbidities and lifestyle factors. The decision support system will take into account all available information, in particular the results from different computational models that are capable both of yielding more effective characterisations of the disease state and predicting the consequences of interventions. The specific challenges in building the DSS tool include the development of the representation, annotation, and integration of heterogeneous data from multiple sources, with a major focus on the visual representation that will assist the clinician in achieving access to, and interpretation of, the data. The objectives of this deliverable are to describe the design of an integrated system capable of co-operating with the EurValve computational infrastructure and displaying all measured and derived data in an intuitive, efficient and easy-to-navigate graphical interface that contributes to the decision process. The available EurValve decision support facilities are listed, and their means of integration into the DSS described, with a focus on detailing the graphical interface to be featured, and the underlying computational infrastructure to be employed.

CONCLUSIONS

Built on an existing decision support tool for heart valve disease, the DSS tool will integrate different concepts and patient-specific measures to improve the management of heart valve disease. The DSS will have as its driving objective the need to help the clinician find the best treatment strategy, including whether and when to intervene, how to choose between open surgery and transcatheter interventions, how to select the best prosthesis and its optimum sizing and - in the case of catheter-based interventions - how to choose the most suitable access route.

1 INTRODUCTION

The primary aim of EurValve is to develop and to deploy a Decision Support System to assist the clinician in providing the optimal treatment strategy for the individual patient. Clinical diagnosis and interventional planning for valve disease should be facilitating by interpreting and exploiting all available information, from personal clinical data, population data, clinical guidelines and simulations.

The primary aims of WP5 are to design and implement the EurValve decision support system, including a case-based reasoning facility, and to define the strategy for integration with the EurValve infrastructure. According to Osheroff (1), a DSS should be designed to provide the right information to the right person in the right format through the right channel at the right time (i.e., when the information is needed). Key questions in designing clinical decision support systems are ***whose*** decisions are being supported, ***what*** information is presented, ***when*** it is presented, and ***how*** it is presented to the user. Also, to gain optimal benefit, clinician users need to understand the system's benefits and limitations. The DSS should be fully understood by the clinician user, efficiently integrated into the daily workflow, and coupled with provider order entry software (2). There is good consensus that DSS can offer great potential to improve the quality of care, but attention must be paid to implementation process, not only for the quality improvement to be realised, but also to avoid negative effects.

The major focus of this deliverable will be on the way to present the user with the entire set of available raw/measured/inferred/derived data (*how*), by keeping in mind the timeline to present the results of the DSS (*when*) but also the priority in which to present the information (*what*). This document focuses on the specifications of the DSS from a software point-of-view. We first give an overview of the current landscape of clinical DSS in cardiovascular interventions and heart valve disease applications, with a detailed report of potential DSS categories. After a description of the current commercial decision support of Therenva (Fig. 1.), we then list the available EurValve decision support facilities and describe how they can be integrated into the DSS, with a focus on the objectives underlying computational infrastructure. Technical issues, development timelines and exploitation factors are also discussed.

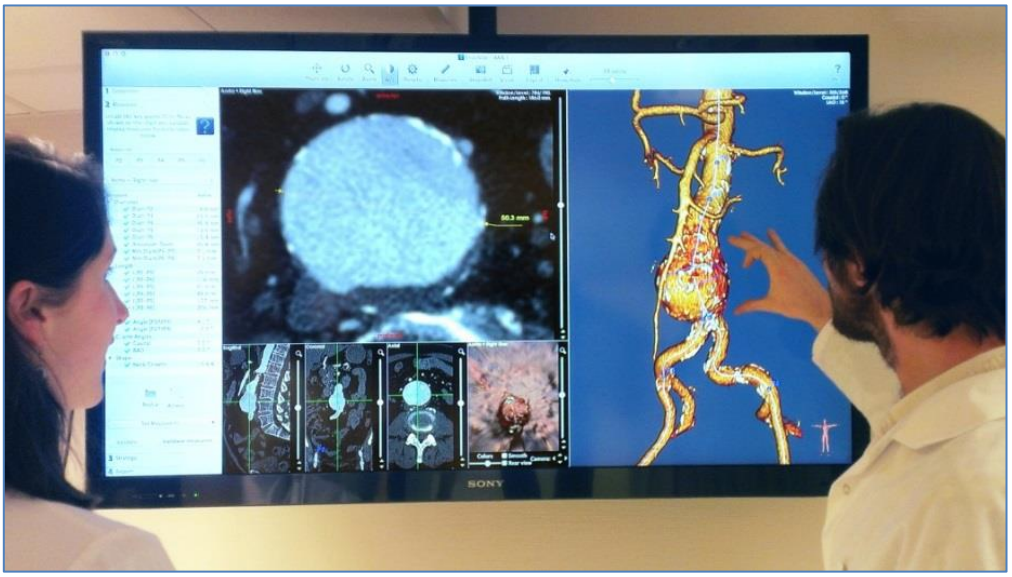

Figure 1: Current Therenva Decision Support Tool - EndoSize®

2 CLINICAL DECISION SUPPORT SYSTEMS

2.1 Landscape

Decision support systems are finding an increasing number of applications in medical science, both within the hospital and in ambulatory care settings. They can provide support to clinicians at various stages and target areas in the care process, from preventive care through diagnosis, planning and treatment to monitoring and follow-up (3). Specifically, they have been widely used to analyse data, give access to practice guidelines and reference information, make decisions, take appropriate actions in the health management of their patients, and also help clinicians avoid "sins of omission," reputed by some authors to be the largest source of medical errors. The most common types of CDSS include drug-interaction checking, preventive care reminders and automatic adverse-event detection.

There are still contradictory results on the benefit of CDSS. Alert-based, or automatic, decision support systems are more successful than on-demand, or user-initiated, systems (4). For instance alert-based DSS have been demonstrated to improve physicians' practice in reducing medical errors and improving adherence to clinical guidelines in various clinical settings (3,5), while other studies reported no significant, or only limited, effects of CDSS (6–8), often because only single sites are studied. Despite these contradictory results, there is a consensus that DSS should be limited to key decisions and provide simple messages, and should offer recommendations in addition to assessment (2). When well-designed and implemented, DSS can assist clinicians with the complex task of optimising intervention, and proven benefits can include reductions in healthcare cost, improved patient safety, and better disease-specific outcomes (9–14). Reviews have suggested that decision support can improve performance, although it has not always been effective (15,16). These reviews have summarised the evidence that computerised decision support works, in part, based on the evidence domain. According to Bates et al. (10), a DSS can provide a "*better cockpit for clinicians, which can help them avoid errors, be more thorough, and stay closer to the findings of the evidence base*."

2.2 Categories of Decision Support System

CDSS can assist clinicians in decision making by taking over some routine tasks, warning clinicians of potential problems, or providing suggestions for clinician consideration (1,17). Data-driven and knowledge-driven approaches are two potential methodologies to develop a DSS, and they can be categorised as knowledge-based and non-knowledge-based (18). In the former, the system comprises a knowledge base plus an inference engine, and user interfaces and decisions are made on the basis of expert knowledge. In the latter, no knowledge base is present and the system relies instead on machine learning algorithms to infer knowledge from past cases.

CDSS can handle different types of input data and encompass a range of options, from general references, through specific guidelines for a given condition, to suggestions that take into account a patient's unique clinical data. CDS can include nationally recommended guidelines at one end of the continuum and customised order sets designed by an individual clinician at the other. Specifically, DSS can be categorised into four types, namely the data-driven, the

document driven, the knowledge-driven, and the model-driven DSS. These categories of DSS use a set of input data that are non-exhaustively listed here:

- ✓ Literature data
  - *Outcomes from registry*
  - *Meta-analysis*
- ✓ Clinical guidelines
- ✓ Image-based anatomical measurements
- ✓ Clinical data
  - *Co-morbidities*
  - *Treatment factors*
  - *Intervention factors*
  - *Post-operative outcomes*
- ✓ Laboratory data
  - *Proteomics data*
  - *Biological data*
- ✓ Simulation-based data
  - *Biomechanical data*
  - *Electrophysiological data*
  - *Haemodynamic data*

2.3 Decision Support in cardiovascular interventions

A wide variety of common cardiovascular conditions could benefit from the application of computerised decision support strategies. This is due to the strong foundation in evidence-based medicine and well-established clinical guidelines in cardiovascular medicine. CDSS have already been successfully implemented in dyslipidaemia screening and treatment, VTE prevention, pulmonary embolism risk stratification, management of atrial fibrillation, stroke management, prevention of coronary artery disease, anticoagulation management, and others.

So far, decision support systems have been mainly applied through risk scores, and preoperative risk stratification is becoming essential to making sound surgical decisions. General risk scoring systems have been developed to predict mortality or major complications after cardiac surgery. The European System for Cardiac Operative Risk Evaluation (EuroSCORE), developed in Europe, is designed to predict the 30-day mortality rate of patients undergoing cardiac surgery (19), and has become the standard by which risk assessment is measured in the scientific literature. A recent update (EuroSCORE II) is currently being validated (20), and the dedicated 18 clinical parameters and associated coefficients from the logistic regression model have been made available (Fig. 2.). A website is also provided for online use (Fig. 3.), where completion of a form results in an automatic risk score generation.

Risk factor	Coefficient	Standard error	z	P ≥ |z|	[95% confidence interval]
NYHA					
II	0.1070545	0.1463849	0.73	0.465	[−0.1798547, 0.3939637]
III	0.2958358	0.141466	2.09	0.037	[0.0185674, 0.5731042]
IV	0.5597929	0.1697565	3.30	0.001	[0.2270763, 0.8925095]
CCS4	0.2226147	0.1462888	1.52	0.128	[−0.0641061, 0.5093356]
IDDM	0.3542749	0.145863	2.43	0.015	[0.0683887, 0.6401611]
Age	0.0285181	0.0065954	4.32	0.000	[0.0155914, 0.0414448]
Female	0.2196434	0.0953505	2.30	0.021	[0.0327599, 0.4065269]
ECA	0.5360268	0.1106046	4.85	0.000	[0.3192458, 0.7528079]
CPD	0.1886564	0.1232126	1.53	0.126	[−0.0528358, 0.4301486]
N/M mob	0.2407181	0.1729494	1.39	0.164	[−0.0982564, 0.5796927]
Redo	01.118599	0.1226272	9.12	0.000	[0.8782539, 1.3589440]
Renal dysfunction					
On dialysis	0.6421508	0.3083468	2.08	0.037	[0.0378021, 1.2464990]
CC ≤ 50	0.8592256	0.1446758	5.94	0.000	[0.5756663, 1.1427850]
CC 50–85	0.303553	0.1240518	2.45	0.014	[0.0604159, 0.5466901]
AE	0.6194522	0.2046001	3.03	0.002	[0.2184433, 1.0204610]
Critical	1.086517	0.147657	7.36	0.000	[0.797115, 1.3759200]
LV function					
Moderate	0.3150652	0.1036182	3.04	0.002	[0.1119773, 0.5181530]
Poor	0.8084096	0.1498233	5.40	0.000	[0.5147614, 1.1020580]
Very poor	0.9346919	0.2917754	3.20	0.001	[0.3628227, 1.5065610]
Recent MI	0.1528943	0.136257	1.12	0.262	[−0.1141646, 0.4199531]
PA systolic pressure					
31–55 mmHg	0.1788899	0.1266713	1.41	0.158	[−0.0693812, 0.4271611]
≥55	0.3491475	0.1676641	2.08	0.037	[0.0205318, 0.6777632]
Urgency					
Urgent	0.3174673	0.1174178	2.70	0.007	[0.0873326, 0.5476020]
Emergency	0.7039121	0.1719835	4.09	0.000	[0.3668306, 1.0409940]
Salvage	1.362947	0.33706	4.04	0.000	[0.7023221, 2.0235730]
Weight of procedure					
1 non-CABG	0.0062118	0.1463574	0.04	0.966	[−0.2806434, 0.2930670]
2	0.5521478	0.1268137	4.35	0.000	[0.3035975, 0.8006980]
3+	0.9724533	0.1463969	6.64	0.000	[0.6855206, 1.2593860]
Thoracic aorta	0.6527205	0.221183	2.95	0.003	[0.2192097, 1.0862310]
Constant	−5.324537	0.1682446	−31.65	0.000	[−5.65429, −4.9947830]

Figure 2: Risk factors and associated coefficients for EuroSCORE II.

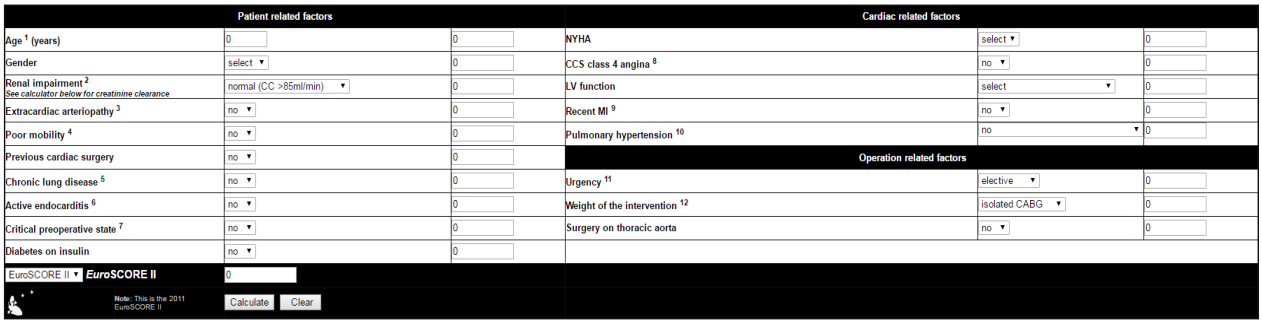

Figure 3: Form for on-line computation of the EuroSCORE II (http://www.euroscore.org).

For now, surgical risk score algorithms are used for patient selection and estimation of short-term clinical outcome in cardiovascular interventions. Statistical risk models are developed using post-data results of previous intervention. However, such risk-scoring systems are more applicable when the preoperative patients' characteristics and treatment profiles are comparable with those on which the system was developed, so even if risk scores are validated worldwide, the data are not homogeneous.

2.4 Decision Support in Valvular Heart Failure

As reported within the ECS guidelines, it has been shown that, in current practice, therapeutic intervention for VHD is underused in high-risk patients with symptoms, justifying the need for careful risk stratification.

Among well-known risk scores, the Society of Thoracic Surgeons' risk models, having the advantage of being specific to VHD, predict the risk of operative mortality and morbidity on the basis of 40 patient demographic and clinical variables (21–23). And, similarly to EuroSCORE, an online form is available for calculating patient-specific risks (Fig. 4.). Other scoring systems have been proposed (24,25), but with relatively poor calibration results. Examples of clinical parameters contributing to these risk scores can be seen in Fig. 5.

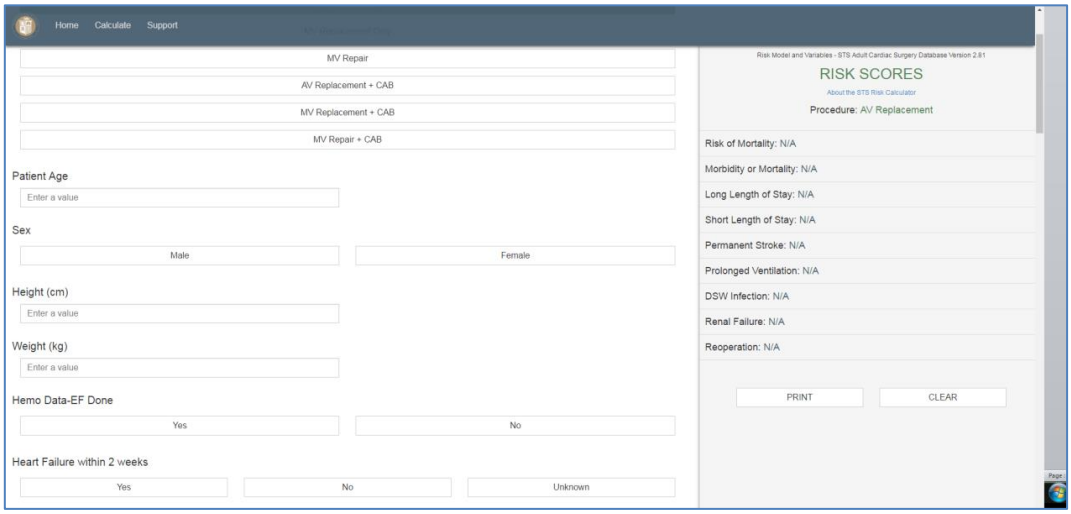

Figure 4: Form for on-line computation of the STS score (http://riskcalc.sts.org/stswebriskcalc/).

Table 1 - **Risk scores**

Variables	*Euroscore **	*STS SCORE **	*Ambler **
Age	+	+	+
Sex	+	+	+
Chronic lung disease	+	+	–
Extracardiac arterial disease	+	+	–
Neurological dysfunction	+	+	–
Heart surgery	+	+	+
Renal dysfunction	+	+	+
Endocarditis	+	+	+
Critical preoperative status	+	+	–
Unstable angina	+	+	–
Ventricular dysfunction	+	+	+
Recent myocardial infarction	+	+	–
Pulmonary hypertension	+	+	–
Emergency surgery	+	+	–
Another surgery rather than coronary artery bypass grafting	+	+	+
Surgery on thoracic aorta	+	+	–
Post-infarction septal rupture surgery	+	+	–
Hypertension	–	+	+
Diabetes	–	+	+
Preoperative arrhythmia	–	+	+
Concomitant tricuspid surgery	–	–	+
Body Mass Index	–	+	+
Valve surgery (aortic/mitral valve/ mitral-aortic surgery)	–	+#	+
Imunossupressor therapy	–	+	–

*(+) Presence of the variable in the score; (–) absence of the variable in the score; * Tools available online - www.euroscore.org; riskcalc.sts.org/STSWebRiskCalc273; www.ucl.ac.uk/statistics/research/riskmodel/index.html*
(#) STS SCORE allows calculating aortic and isolated mitral valve surgeries; combined surgery cannot be included in the STS, only in Ambler.

Figure 5: Comparisons of included clinical parameters in major VHD risk models

2.4.1 Aortic stenosis

Aortic Stenosis (AS) is the most common valvular heart disease, and aortic valve replacement (AVR) is the standard therapy for severe AS. Early replacement is recommended for all symptomatic patients with severe AS who are considered suitable for surgery, as the disease is progressive and there is no medical therapy that is able to improve outcome. AVR allows total control of the tools, the implantation site and the anchoring of the prosthesis by the surgeon. Although surgical aortic-valve replacement improves symptoms and survival, there are other subgroups of patients (e.g. advanced age, poor left ventricular function) who are at increased risk of operative complications. For those patients, a less invasive treatment may be a more desirable alternative.

Compared to open-chest valve surgery, minimally-invasive trans-catheter aortic valve implantation (TAVI) is an emerging technique that is especially suitable for high-risk patients with severe aortic stenosis, but which also has the potential to be applied to lower surgical-risk patients in the future (26). However, TAVI is not available at all centres, and the long-term durability of TAVI valves has yet to be established. In the PARTNER trial, important differences in morbidity were observed; surgical AVR was associated with increased bleeding and related complications, and stroke was more common after TAVI (27). Despite some controversial results, TAVI has been shown to be non-inferior when compared with standard AVR, and both the European Society of Cardiology (ECS) and the American Heart Association in collaboration with the American College of Cardiology (AHA and ACC) provide practice guidelines for the treatment of severe aortic stenosis and the selected use of TAVI. They both recommend a collaborative decision-making process for patients with symptomatic aortic stenosis.

Clinical outcomes following TAVI are directly related to appropriate patient selection and valve choice. Known complications include paravalvular leaks, stroke, atrioventricular blocks, coronary obstruction and annular rupture. These adverse effects may be reduced with improved patient selection, intervention planning, and aortic sizing with the use of image analysis tools, making imaging assistance an essential task for proper decision-making. TAVI requires meticulous preparation, and inaccurate pre-operative assessment can severely impair the success of the procedure.

Before surgery, echocardiography and Computed Tomography (CT) are key techniques used to confirm the diagnosis of aortic stenosis, to assess LV function and wall thickness and to provide prognostic information. Such imaging provides important information on the access route but also on the individual valvular anatomy, such as the degree and distribution of calcification, leaflet anatomy, and the dimensions of the aortic valvular complex (28). This step is crucial, as there is a consensus that different types of valve prosthesis (size, shape) and repair techniques will have different functional results. This is in complete contrast to standard AVR, where the surgeon has an opportunity to size the annulus directly, using a probe. Post-operatively, imaging is also required to identify immediate complications and assess outcomes.

A number of studies have proposed imaging pipelines to extract the aortic valve anatomical parameters and derived clinical measurements that are important for calculating the geometric constraints for the size and position of the implant. While solutions using manual interactions

have been proposed to guide TAVI planning (29), automatic processing may have a positive impact. Many studies focused on the segmentation of the thoracic aorta (30,31) in CTA, while others focused on aortic root segmentation (32). Automatic detection of key anatomical landmarks (coronary arteries, aortic leaflets, or aortic commissures) may also be helpful, and several approaches have already been proposed (33–35).

While careful imaging of the anatomy provides vital information for TAVI sizing, this population of patients would greatly benefit from a more complex decision support system for proper decision-making. Statistical models are restricted in the number of input parameters, and complications are difficult to generalise. At present they 'limit' medical decisions 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 in a given patient. Moreover, tools and prostheses are evolving, and new models cannot benefit from statistical risk assessment since post-operative data are not available. Due to the lack of long-term results, TAVI is restricted to high-risk and inoperable patients based on risk scoring using the STS score or the EuroSCORE. Both these scoring systems have been tested in TAVI populations, showing a superiority for the STS score (36,37). Although a EuroSCORE > 20 has been suggested as an indication for TAVI therapy, an STS score >10% is more realistic (38). And although a TAVI risk scoring system implementing geriatric and anatomical variables is still lacking, the addition of a wide variety of data within complex simulation-based and predictive models would be crucial for providing appropriate **patient selection**, **valve and access route choices**.

2.4.2 Mitral regurgitation

Mitral regurgitation (MR) is the second most frequent valve disease in the EU, and there is a trend that valve repair is preferred over valve replacement in surgical therapies. Catheter-based interventions using either transapical or transfemoral access have been proven to be effective in reducing mitral regurgitation or treating mitral stenosis and are associated with low rates of complications. Similar to AS, catheter-based techniques may be a lower risk alternative treatment for high-risk patients, and the same sizing issues are present. Multimodal evaluation of the prosthesis type and size using echocardiography and CT scans is mandatory, as not all valve/ring models are amenable to transcatheter therapy, highlighting the need for proper pre-operative sizing.

No specific risk scores have been proposed for trans-catheter mitral valve interventions, even if some important predictors have been identified (39,40). As careful patient selection remains crucial and no risk models are currently available, the need for a DSS is apparent.

2.5 Current Commercial Decision Support – EndoSize®

2.5.1 General presentation

Therenva develops and markets EndoSize® (CE-marked and FDA-approved), a software system for cardiovascular sizing that provides surgeons and cardiologists with an efficient tool for choosing the optimal procedure, strategy and implant device based on patient CT images. EndoSize® enables physicians and clinical specialists to select patient CT scan studies from various DICOM data sources, view them, and process the images using a comprehensive set of tools. EndoSize® is intended to provide a clinical decision support system during the preoperative planning of endovascular interventions such as the selection of the endoprosthesis and the best interventional approach. EndoSize® currently contains five modules dedicated to each type of endovascular intervention:

- ✓ **EVAR**: planning and sizing for endovascular aortic aneurysm repair
- ✓ **TEVAR**: planning and sizing for thoracic endovascular aneurysm repair
- ✓ **FEVAR**: planning and sizing for fenestrated aortic aneurysm repair
- ✓ **TAVI**: planning and sizing for transcatheter aortic valve implantation
- ✓ **Peripheral**: planning and sizing for peripheral endovascular procedures

The general functionalities are:

- ✓ Import and reading of CT scan images in DICOM format.
- ✓ Three-dimensional reconstruction of the CT scans images (Fig. 6).
- ✓ Visualisation of CT scan images in every planes (Fig. 6).
- ✓ Highlighting of vascular anatomy and morphology and vascular pathology by imaging processing (extraction of surface mesh and segmented analysis).
- ✓ Automatic and interactive extractions of length and diameter measurements of arteries from CT scan reconstructed images.
- ✓ Decision-making aids for sizing of endografts.
- ✓ Presentation of size-corresponding endografts available from manufacturers (optional).
- ✓ Purchase order edition (optional).

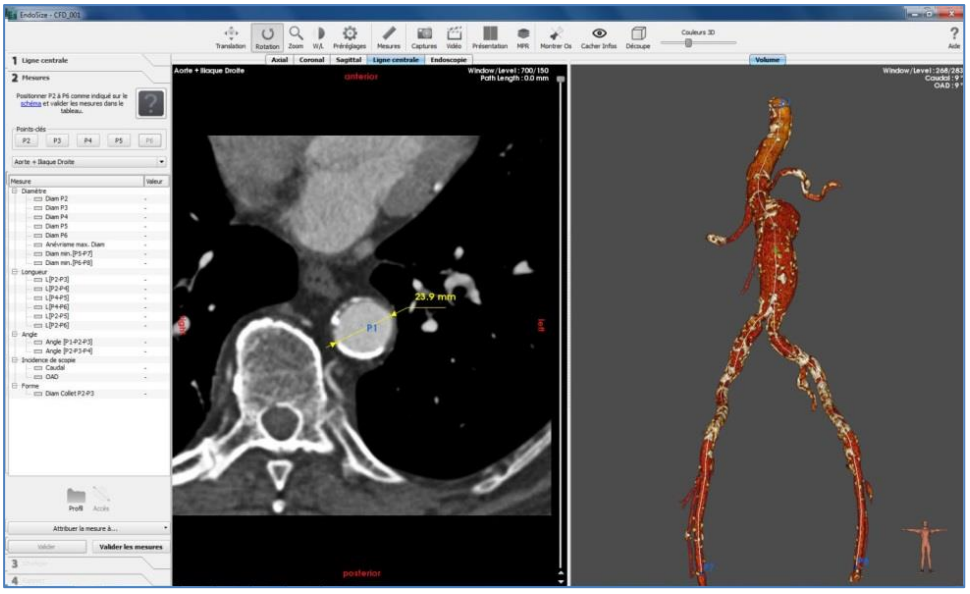

Figure 6: Visualisation of 2D section and 3D reconstruction

2.5.2 TAVI module

In the **TAVI module**, the user is guided through the choice of the optimum therapeutic strategy that allows for selection of the best aortic valve prosthesis and accurate planning of the deployment. After the selection and visualisation of the patient within the patient manager (Fig 7a), the module is composed of 5 steps.

- The workflow begins with a semi-automatic aorta artery segmentation and centrelines extraction (Fig 7b) based on the placement of 3 keypoints. The segmentation of the arteries simplifies anatomical measurements along the vessel centrelines.

- After validation of the segmentation, an automatic detection of leaflet and initialisation of the valve plane is proposed (Fig 7c).

- After potential manual adjustment of the virtual basal ring, the user has access to a complete set of tools for key anatomical measurements of the aortic root (Fig 8a). Specifically, anatomical measurements such as basal ring, sinus of Valsalva and ascending aorta diameters, or coronary arteries heights and STJ-annulus distance. Other tools such as calcification scores, c-arm position planning or virtual device visualisation are also available.

- After the aortic root measurement step, three main access routes are currently considered and can be planned: the femoral artery, the subclavian artery and the apex of the heart (Fig 8b).

- Finally, the user enters the strategy step, where the final report is generated (Fig 8c). The physicians can visualise a simple representation of the endoprosthesis on the patient scan in 3D and they are automatically warned if the selected endoprosthesis is inadequate.

The report generates the proper sizing worksheet and makes pictures ready to print or send. Video can be easily added for clinical case presentation. EndoSize® records the sizing process and manages patient data follow-up for rigorous traceability.

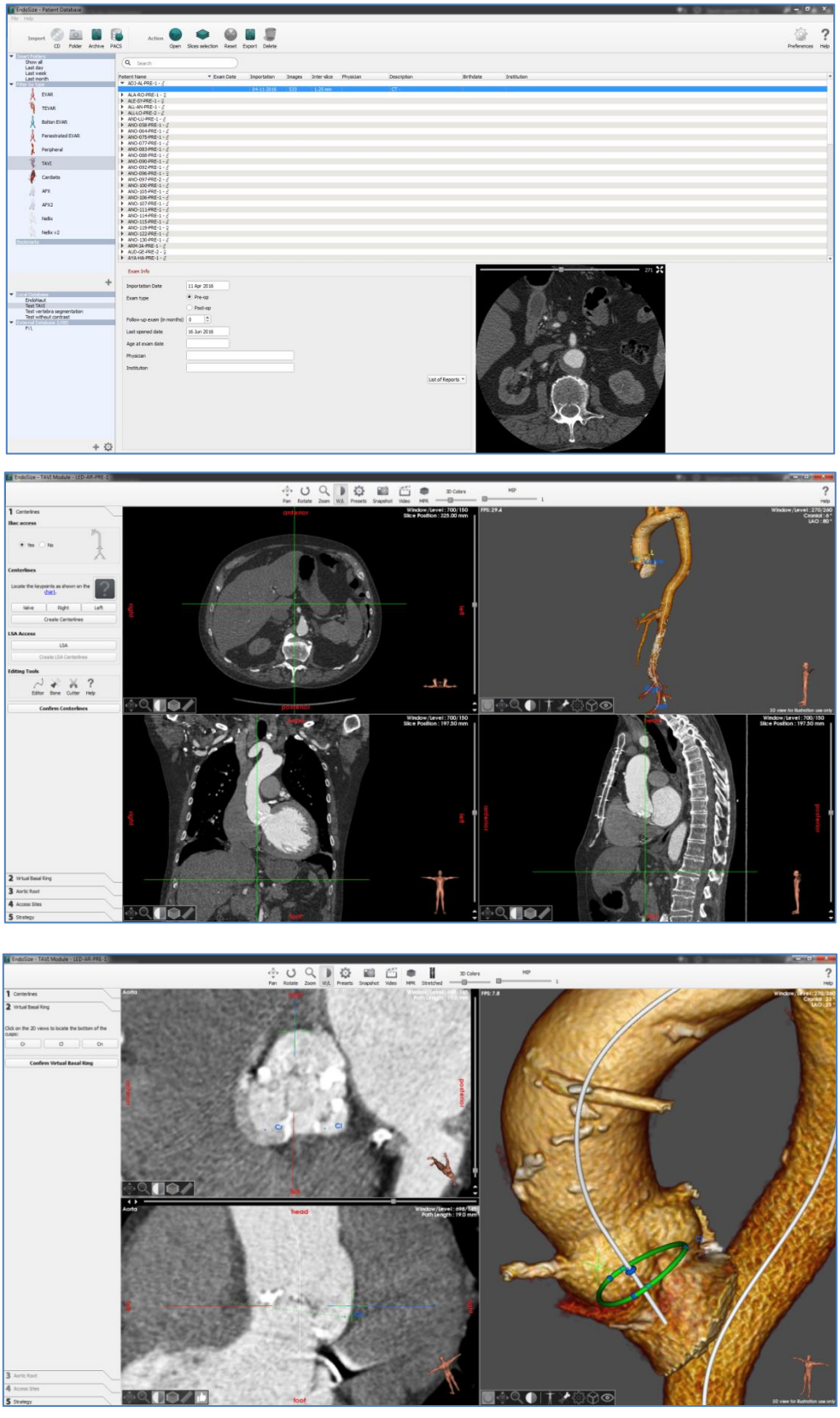

Figure 7: Endosize® workflow (1).
From top to bottom: Patient manager (Fig 7a), semi-automatic aorta segmentation and centrelines extraction (Fig 7b), automatic detection of leaflets and virtual basal ring visualisation (Fig 7c).

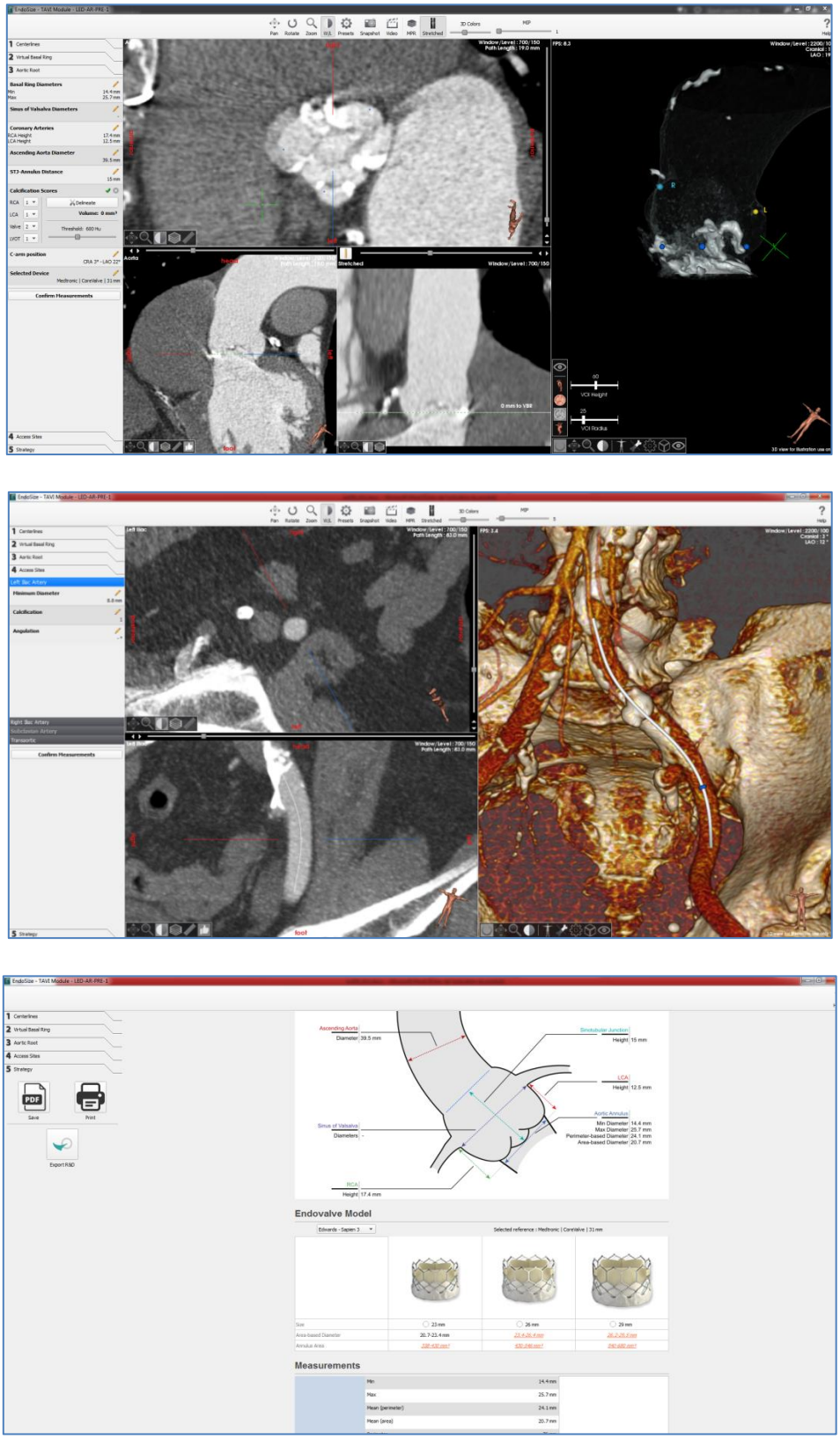

Figure 8: Endosize® workflow (2).
From top to bottom: Aortic root specific measurements (Fig 8a),
iliac access measurements (Fig 8b), final summary and strategy (Fig 8c).

2.5.3 Software/hardware

The EndoSize® software runs on any standard Windows or Mac OSX based computer that meets the minimum requirements (Table 1), and does not need additional resources. It works with DICOM CT scan images and can access multiple DICOM data files and PACS servers (Fig. 9). The entire EndoSize® solution is built on C++ architecture, and the framework is composed of several libraries which themselves depend on open-source libraries, including VTK, ITK, Qt, Dcmtk, OpenSSL, Zlib.

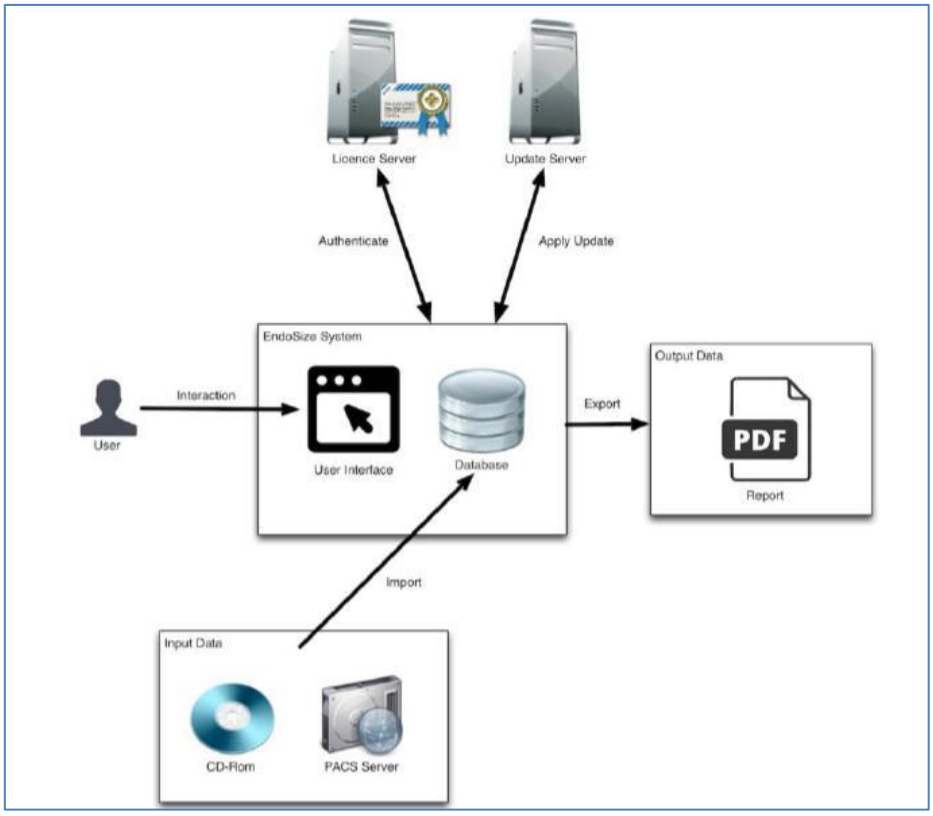

Figure 9: System architecture

Component	Minimal System Requirements
Operating System	Mac OSX 10.6 or greater, Windows 7/8/10 64 bits
Processor	2 Ghz DualCore
RAM	4 GB
Hard Drive	500 MB (free space for patient data not included: 500MB per patient)
Screen Resolution	1280*768
Graphics	Graphics card with 256 MB of dedicated memory

Table 1: Minimum characteristic for hardware

3 EURVALVE DSS & SOFTWARE INTEGRATION

As described in the previous section, AS and MR would greatly benefit from a multi-level DSS. The goal of EurValve is to create a modelling-based DSS that allows the simulation, outcome assessment and risk comparison of different treatment strategies. The computational models will offer more effective characterisation of the disease state and prediction of the effects of intervention. We believe that the DSS will have major impact on patients with:

- ✓ Borderline indications for treatment
- ✓ Complex haemodynamic conditions
- ✓ Valve geometries that are subject to valve repair

The DSS tool will facilitate the representation, annotation, integration and visualisation of heterogeneous data from multiple sources, and will make effective use of the data that is available for the patient, by fully utilising routinely-collected information. This section will describe the full list of concepts and features that will be integrated into the DSS, with a focus on the technical specification and results presentation via the graphical interface. Building on the state-of-the-art presented in the previous section, the selected concepts are intended to answer these clinically-relevant questions:

- ✓ What is the best treatment for my patient?
  - Intervene or not?
  - If intervention, optimum timing?
  - If intervention, open surgery or transcatheter?
- ✓ Is my patient at high risk of complications?
- ✓ In the case of a catheter-based intervention:
  - Which prosthesis should I choose?
  - Which prosthesis size should I choose?
  - Which is the best access route?

3.1 Facilities List

Table 2 summarises all measures and concepts that are expected to be available for inclusion in the DSS. In some cases the available information is important mainly for the development of other project features, and is less relevant to the clinical user; ultimately these will not be handled by the DSS. For example, this is the case for components from the knowledge generation phase, which includes sensitivity analyses, the tuning of the flow simulation system, proteomics data, the machine learning process (as distinct from the results) and the ROM generation steps. It is however very different for the predictive case processing step, where almost all components will provide data or models.

Table 2 and Figure 10 give an overview of the interconnections with other WPs, setting the scene for the detail in the later subsections. In addition, Annex 1 presents the set of high-level user stories that are currently considered appropriate for the exploitation of the associated concepts, but this list is subject to modification and further refinement.

Measures/concepts	Task	User story	Illuminates which question?
Literature data	T4.3	DSS-9, DSS-10	➢ Which references are available?
Guidelines	T4.3	DSS-11, DSS-12	➢ Which intervention strategy? ➢ High-risk patient?
Risk scores	T4.3	DSS-13, DSS-14	➢ Which intervention strategy? ➢ High-risk patient?
Data infrastructure ✓ Patient-specific data ✓ Segmentation ✓ Predictive models – ML ✓ Sensitivity analysis – results	 T2.1 T3.2 T3.1 T3.4	DSS-1, DSS-2, DSS-15	➢ Which intervention strategy? ➢ High-risk patient? ➢ Which prosthesis (TAVI)? ➢ Which prosthesis size (TAVI)? ➢ Which access route (TAVI)?
Numerical simulation – 0D model	T3.3	DSS-16	➢ Which intervention strategy? ➢ High-risk patient?
Numerical simulation – 3D model + ROM	T3.3 T3.6	DSS-17	➢ Which intervention strategy? ➢ High-risk patient?
CBR	T5.3	DSS-18, DSS-19, DSS-20	➢ Which intervention strategy? ➢ High-risk patient? ➢ Which prosthesis (TAVI)? ➢ Which prosthesis size (TAVI)? ➢ Which access route (TAVI)?

Table 2: Enhancements in detail

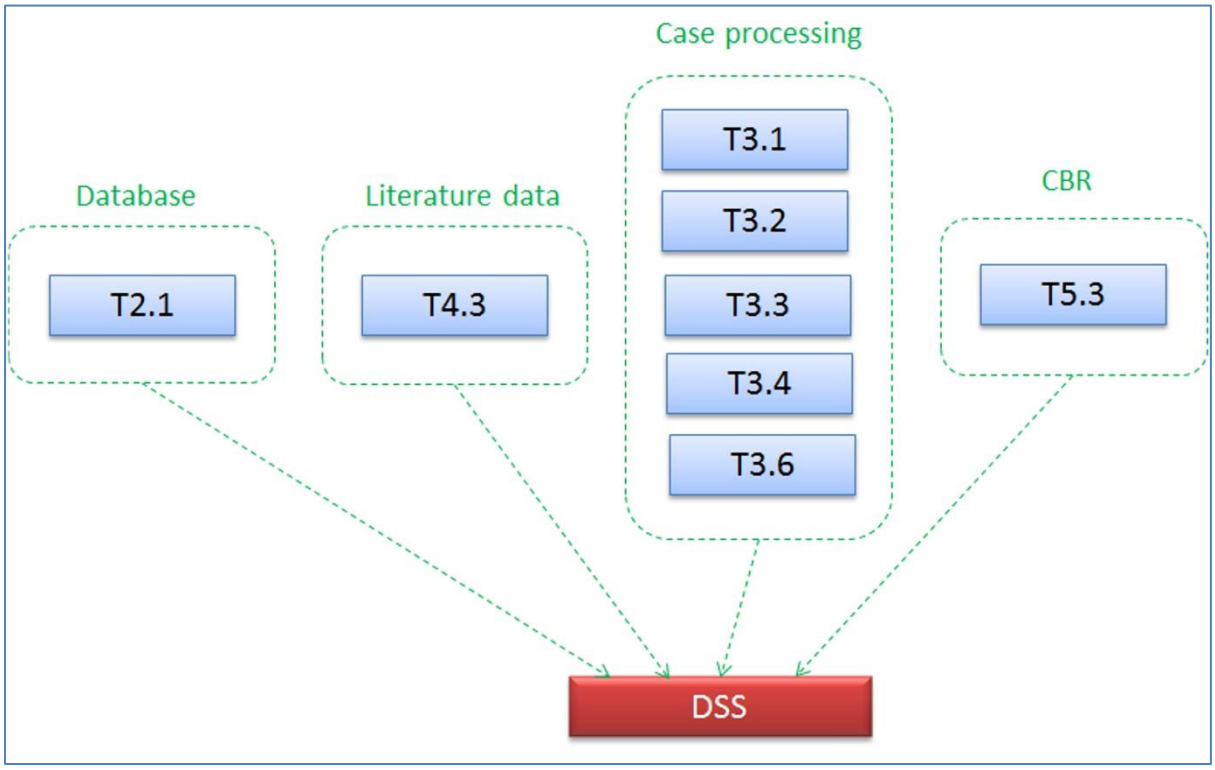

Figure 10: Interconnections, showing technical overlaps with other WPs

3.1.1 Literature data

3.1.1.1 Feature/concept

The literature-related feature of the DSS will provide easy context-sensitive access to a set of publications that could be opened next to each main concept/measure. This set of publications will be mainly selected from clinical guidelines, review, meta-analysis, or important clinical trials. As an initial step, hyperlinks to these documents will be stored in a database and a later development will introduce direct access to the documents themselves, if publications are available through open access or if authorisation to share is obtained. In cases where access is denied, the use of structured summaries will be considered. If the EurValve project itself develops additional knowledge and rules, through extraction and analysis of literature data or otherwise, and that can be usefully formalised for clinical deployment (for example in the form of a decision tree or a rule set), this information will also be available.

3.1.1.2 Technical issues

The provision of hyperlinks to specific publications is straightforward. To provide the documents themselves, a literature repository must be accessible from a user's machine. During the life of the project, the DSS will maintain connectivity with the central project infrastructure enabling quick and easy retrieval; to facilitate this functionality in a disconnected stand-alone configuration it will be necessary for documents also to exist in a local database, and this functionality will additionally be provided, facilitating the sustainability of the DSS.

3.1.1.3 Graphical interface

Literature retrieval will require no complex graphical interface, and hyperlinks or .pdf links will be made available adjacent to all major measures and concepts.

3.1.1.4 Interactions with other WP

Task 4.3 within WP4 is responsible for activities relating to literature analysis, and close cooperation with the T4.3 team will ensure the provision of relevant publications sets for each main concept and measure. This set of publications will be available at PM15 for D4.4, 'Literature and guidelines analysis and recommendations'.

3.1.2 Current guidelines

3.1.2.1 Feature/concept

Clinical Guidelines are the knowledge base for the mechanism relied upon almost universally for the dissemination of the rapidly increasing body of clinical knowledge. Although it is anticipated that clinicians are completely familiar with the Guidelines applicable to their chosen discipline, the documents are often complex, and are subject to regular review, so there is significant merit in formalising their content, especially for use by young clinicians and for training purposes. Within the ECS guidelines, a decision tree is available for each of the pathologies of interest, aortic stenosis (Annex 1-A) and mitral regurgitation (Annex 1-B). In each decision tree a list of hierarchical rules is defined and therapeutic recommendations are proposed, currently including open surgical repair and trans-catheter intervention.

3.1.2.2 Technical issues

Implementation of a mechanism to present the ECS guidelines presents no inherent challenges; the source information is freely available to the community with no restrictions.

3.1.2.3 Graphical interface

Dynamic, user-friendly, interactive decision trees will be implemented, with both global representations and zoomed views at each level of the tree.

3.1.2.4 Interactions with other WP

Only limited interactions with other WPs are required for this feature. Feedback from clinical partners on the general ergonomy of the proposed interface will be important, as indeed it will be for all features (see clinical consultation below).

3.1.3 Risk scores

3.1.3.1 Feature/concept

Risk scoring systems have been developed to predict mortality and major complications from cardiac surgery. The two major risk scores used in the context of VHD are the EuroSCORE and the STS score, described in sections 2.2, 2.3 and 2.4. Both scores will be implemented.

3.1.3.2 Technical issues

The EuroSCORE partners have published the underlying regression models, making it possible for them to be reproduced. The position with regard to the internal regression model for the STS score is, at the time of writing, less clear, though implementations are known (41). Investigation is under way and it may be the case that negotiation over copyright will be required. It is noted that such scoring systems are subject to regular review and that recalibration is required to maintain currency of results.

3.1.3.3 Graphical interface

A data capture mechanism for both directly-entered information and data held in the central infrastructure data store will be implemented. For EuroSCORE, 18 clinical parameters are required (Fig 2). For the STS score (assuming accessibility), 40 demographic and clinical parameters are needed.

3.1.3.4 Interactions with other WP

No strong interactions with other WPs are anticipated for this feature. As with the Guidelines, feedback from clinical partners on the proposed graphical interface and its ease-of-use will be sought.

3.1.4 Data infrastructure

3.1.4.1 Feature/concept

The Data Infrastructure has at its heart a repository of patient information, including data from all heterogeneous sources which could be directly measured and processed from imaging, completed from information held in the EHR (demographic data, co-morbidities, lifestyle factors), or inferred and processed from machine learning. The data can be characterised as numerical, text, categorical (ordered), or Boolean. Examples of numerical data include blood count, coagulation parameters, age, size, and specific physiological measurements. Text data comprises descriptive items regarding the patient's pathological or surgical history as well as, for example, possible allergies. Ordered data includes attributes that measure degrees of intensity, for example the amount of calcification, or of regurgitation, whilst Boolean data confirms or denies the presence of an attribute, for example the existence of vascular tortuosity or the presence of coronary flow damage. The data infrastructure concept is further divided into input and output data.

For **input data**, a data capture mechanism for both directly-entered information and data held in the central infrastructure data store will be implemented. CT-based anatomical data will be automatically transferred from the sizing within EndoSize®, whilst the facility for a range of segmentation alternatives, including those developed within WP3, will be developed. Whilst it is acknowledged that early discussions on the possible use of MR image data are underway, the anticipatory development of an MR segmentation service is considered out of scope, matching the view of the WP3 group.

For **output data**, it is clear that the objective is not to propose the fullest possible list of available data to the user, but rather a condensed set of clinically-relevant output data (mainly cardiac physiological parameters such as ventricular afterload, end diastolic volume and similar) which can be analysed by the surgeon and transformed into a clinical decision. To this end, Table 10 from D4.1 (Annex 3), which has been further extended in D3.1, has been proposed. In addition, each data item will be identified by a 'flag' system that describes its provenance: raw, inferred, or processed. Specifically, the derived information includes anatomical parameters, other parameters that allow an effective characterisation of the disease state, and parameters that will predict the effect of intervention.

Beyond consideration of the presentation of output data, there is the concept of '**recommendations**'. In the literature, there is consensus that a DSS that recommends actions is more effective than a DSS that simply provides assessments. It is anticipated that in WP6 EurValve is likely to develop new knowledge, and any such outputs might legitimately be presented in the DSS as **observations**, requiring user interpretation. The ability to move from observation to recommendation is a separate step, beyond the scope of EurValve, but, where knowledge is already cast as a recommendation (for example in a clinical guideline), it can reliably be presented as such. Accordingly, such a presentation facility will be implemented, and outputs will be categorised as observations or recommendations as appropriate.

3.1.4.2 Technical issues

Several technical issues arise from this concept:

- Whilst during the project the DSS tool requires access to the data within the infrastructure-based data system, post-project this is no longer the case. A range of possible access mechanisms exists, from - at one end of the spectrum - a full implementation of web-service-based connectivity and dynamic SQL query creation, to - at the other end - a focused export/import system tailored to a precise DSS data subset. At the time of writing the optimum solution is under review with the project's Architecture Team; project partners have established expertise in all such approaches, and the final mix of techniques will be influenced by speed, convenience, reliability, flexibility and post-project utility, together with the practical requirements during both the developmental and operational phases of the project. Irrespective of this, the independent DSS system will require self-contained local data mechanisms.
- The EurValve project recognised the need for sophisticated segmentation, a feature not currently supported in EndoSize®, and it is a WP3 task to deliver such a system. Therenva, mindful of the need to guarantee support for a fully-exploitable outcome, recognises the need, in some exploitation scenarios, to allow for alternative mechanisms, and will therefore implement a flexible system that will comprehensively support the WP3 solution whilst facilitating alternative approaches should the need arise.
- In similar vein, Therenva has identified the possible need to allow for an exploitation pathway that makes use of an independent machine learning solution. Accordingly, the constructed mechanism will allow direct access to information generated by the WP3 mechanism (however implemented, after the recommendations of the Architecture Team), whilst retaining the possibility of an independent approach using an alternative system for the missing-data prediction engine.

3.1.4.3 Graphical interface

Each measure and concept will be rendered separately identifiable (probably by colour-coding) according to its provenance (measured or inferred). Each such measure, instead of being displayed in a simple table with its associated information, will instead be displayed on its own specific colour-coded axis, together with a representation of the possible range of the data (minimum/maximum), the dedicated measured/inferred value and its confidence interval, calculated by the sensitivity analysis (see 3.1.6). In addition, clinically-relevant literature (see above) will be linked to all such concepts.

3.1.4.4 Interactions with other WP

WP4 will provide data, the majority of which will be patient-specific, including medical images, patient records, disease relevant measurements, or pervasive monitoring data. WP3 will provide the key concepts and measures to be proposed to the user. Extensive information will be transferred from WP3 to WP5, as in principle almost all WP3's derived data can be useful to WP5 (T3.1, T3.2, T3.3, T3.4, T3.6).

3.1.5 Case-based reasoning

3.1.5.1 Feature/concept

The DSS will include the facility to perform Case-Based Reasoning (CBR) against the de-identified data held in the project's data repositories. The objective of CBR is to provide the practitioner with an easily interpretable selection of the cases most relevant to the current candidate patient, and the technique makes the assumption that past experiences may be useful in solving similar current problems. As case histories have long been essential in training healthcare professionals, and reasoning from examples is natural for them, automated CBR systems have been developed for the medical domain, and several examples have been reported in the domain of diagnosis and treatment (42–45). Some relevant recent systems have also used hybrid approaches, which integrate additional artificial intelligence techniques such as rule-based reasoning (46–48). The feasibility of designing a CBR for transcatheter aortic valve implantation has been recently shown, but this work did not focus on investigating similarity functions and only simple representation of cases were considered (49). The complete CBR solution cycle is generally based on four steps (retrieve, reuse, revise and retain) (50). The retrieve step is mandatory, and requires data processing to evaluate reliably the similarity between cases and to recover relevant past cases. The other steps are employed optionally, according to the application, and require user decisions on reuse and revision, and on retention of cases after the application and evaluation of the solution. The EurValve DSS tool will include a purpose-built interface to facilitate the use of these steps in the integration of clinical expertise in the decision process.

Some data can be uncertain (for example, due to imprecision of measurement) or imprecise (for example, artery tortuosity is often represented by enumerated types such as *No*, *Mild*, *Moderate*, *Severe…)*. To overcome this problem other techniques such as fuzzy logic may be applied (51,52). Another frequent problem in CBR systems applied to the medical domain concerns missing data, and again some techniques to deal with this problem already exist (53). In some published work, the 'best' similar case is obtained by applying weightings to the similarity results for each attribute, and various approaches have been used. The weight of attributes can for example be defined using an evolutionary approach (Genetic Algorithm) (45), or with rule-based reasoning (46), or by medical experts (53). The choice of attributes, and consequently of similarity measures, represents an important issue in the retrieval stage, and the selection of input factors is currently under consideration as part of the LTSI work on similarity metrics.

3.1.5.2 Technical issues

A CBR engine will be developed with a focus on the 'retrieve' and 'retain' steps, which will be integrated into the current EndoSize® framework. The similarity between patient and image characteristics (in the blue group *Description* in Figure 11, for example) will be exploited to provide the user with relevant information about diagnosis or treatment (the purple group *Solution* in Figure 11) and also to take into account the procedural outcome of similar patients in the database (the yellow group *Result* in Figure 11). In this example, the results proposed by the CBR in the *Solution* group are focused on the three critical decisions: Which Vascular access? Which Valve model? Which Valve size? When interviewed, most clinicians consider

that the success or the failure of the intervention is highly dependent on the optimum selection of these three attributes.

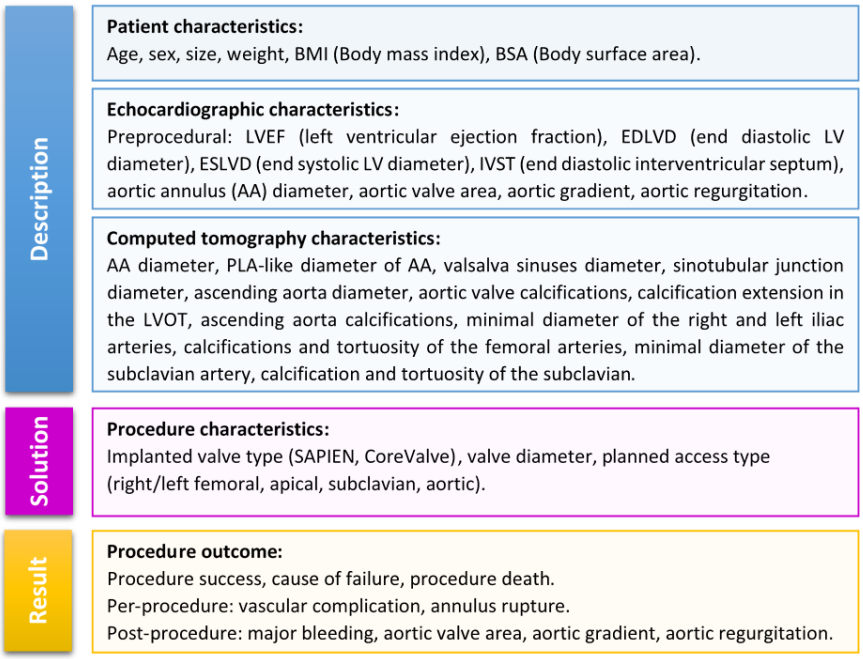

Figure 11: Example of case structure with relevant features.

To improve the retrieval step, work will be carried out on similarity measures themselves, and also on the extraction of significant features. Different similarity measures can be used according to the type of the data (numerical values, Boolean values, quantitative values or symbolic values) (54). The data can result from patient descriptions or from the acquisition of image data and the extraction of measures (local descriptors). To obtain similar cases, a simple weighting on relevant attributes or descriptors will initially be examined, which will rely on the definition of the weights according to a decision tree created from available guidelines. The retrieve step will be further strengthened through the study of new global shape descriptors (morphology and motion, for example). Complementing the techniques that take into account data uncertainty, the use of simulated data from specific anatomical and mechanical models will also be considered. Finally, a basis for the number of similar cases to be presented to the user will be chosen in consultation, and choices include a distance threshold, a percentage of those found, or fixed number.

For data access, again a dual mechanism will be implemented, in which both infrastructure-based methods and a local database will be featured. Again, the method of interfacing with the central system will agreed with the Architecture Team. One particularity of the CBR engine is that not all data from the patient will be required to process cases; the subset to be used is under consideration as part of the work in T5.2.

3.1.5.3 Graphical interface

A specific user interface will be provided to facilitate interpretable visualisation of the summarised data derived from the retrieved cases (an example is shown in Figure 12). With

the most similar case(s) identified, relevant retrieved information will be displayed, including the type of valve, the approach, and the mid- and long-term outcomes (for example, re-intervention). Where clinically relevant, it could also include a summary of the patient data and follow-up, as well as key images. Again, instead of a simple tabular approach giving relevant procedural and outcome data, a colour-coded graphical system with information to highlight low-, medium- or high-risk chances of complications will facilitate direct visual inspection, and will also highlight other attributes, including choice of intervention, type of valve and access route (or, in case of TAVI, intervention choice). It will provide an easy means to appreciate the degree of similarity and the solution / outcome dispersion, and to compare the attributes of similar cases. Additional information will also be displayed, including a confidence measure reflecting the status of the attributes (informed, missing, estimated) considered in the retrieve step (Figure 12), and a warning if the treatment of any of the similar patients did not follow the guideline recommendations.

At the end of the CBR retrieval step, the final graphical display will also allow retention of the case and inclusion in the local database (Figure 13). The necessary tools to remove cases and add procedural characteristics and post-operative outcomes will also be provided.

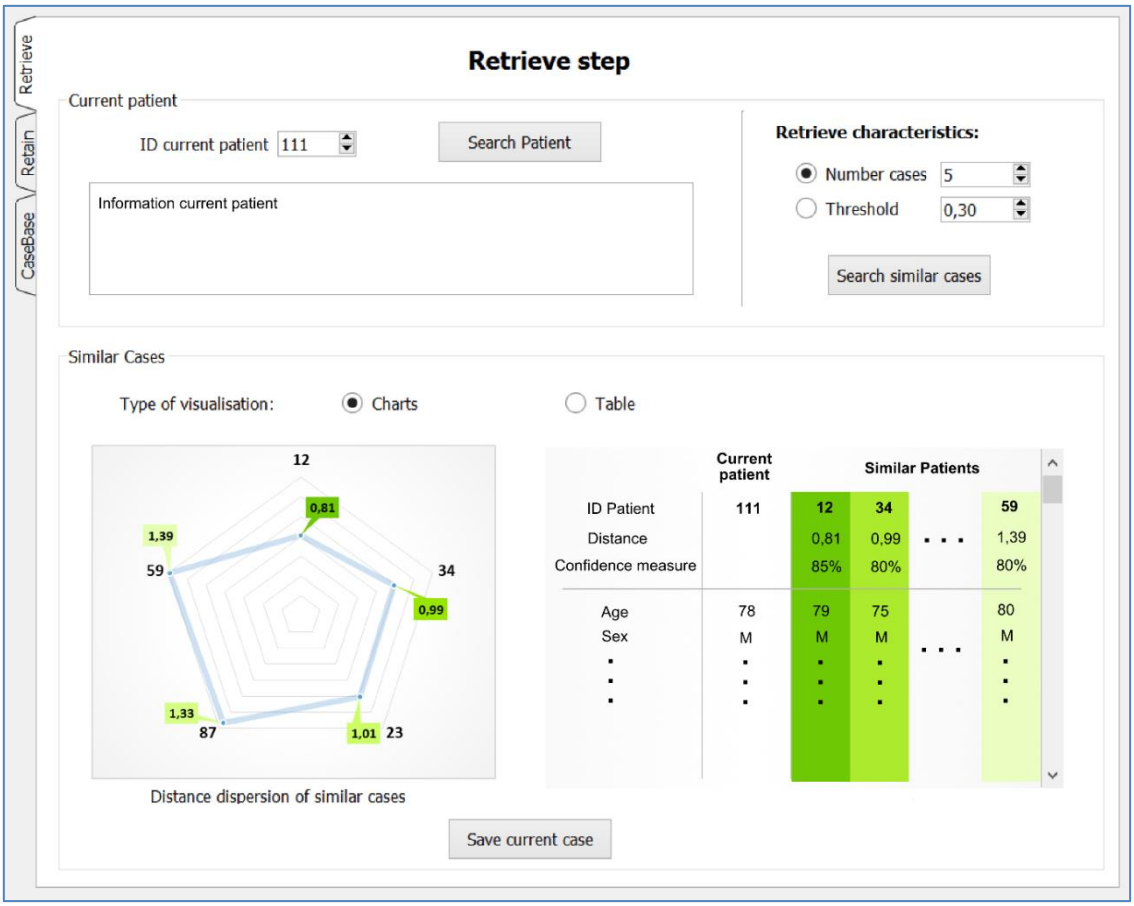

Figure 12: Example of CBR interface for the retrieve step.
Firstly, the user must choose the current patient and secondly must search the similar cases. This example shows a possible illustration with a dedicated chart based on the distance dispersion of the similar cases. A table is also proposed to compare the different attributes of the retained cases.

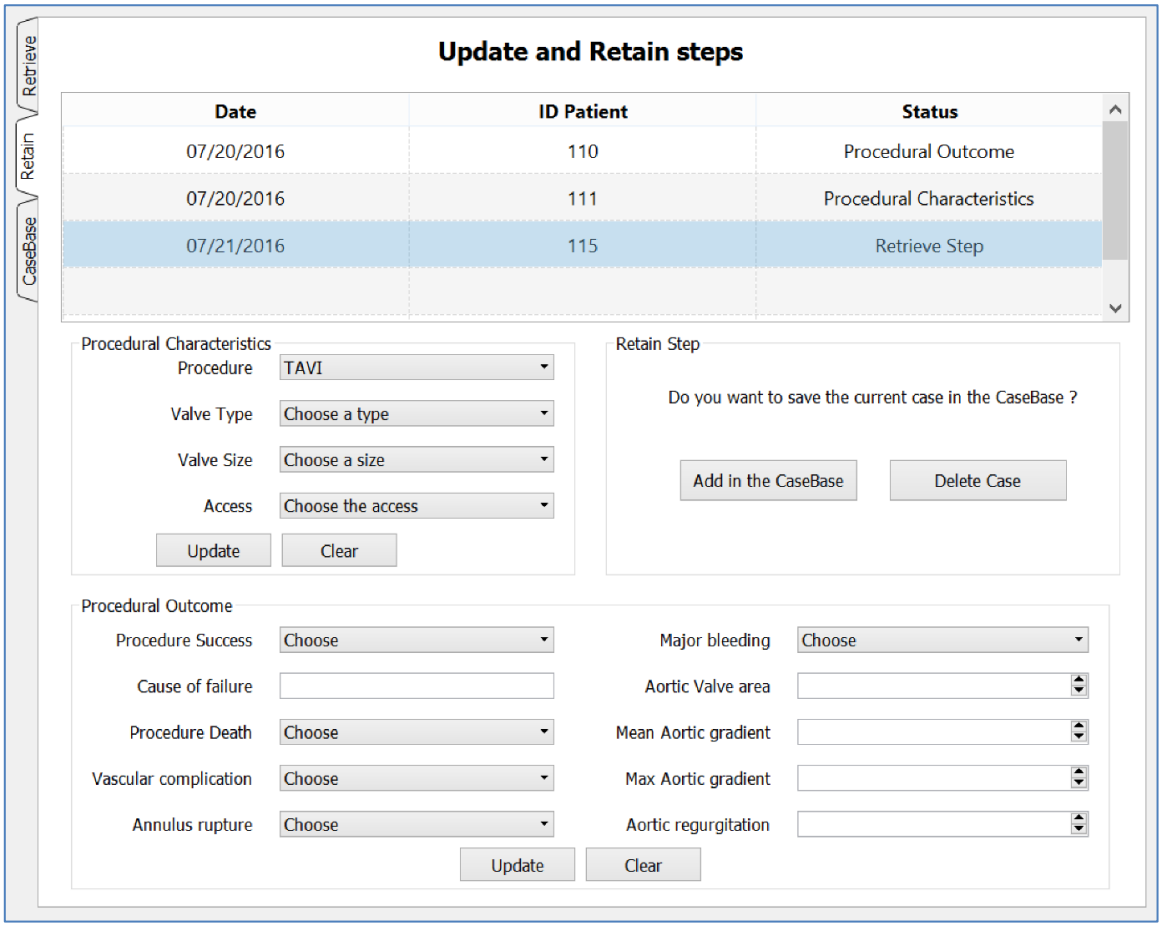

Figure 13: Example of CBR interface for the retain step.
The user can complete a case with the procedural characteristics and outcome available after the retrieve step. Next, the user can choose to add the case in the case base or to delete it.

3.1.5.4 Interactions with other WPs

T4.2 will provide the core CBR system and new similarity metrics, and constant liaison with LTSI will ensure a satisfactory outcome, as part of their continuous collaboration with Therenva.

3.1.6 Numerical simulation – 0D model

3.1.6.1 Feature/concept

The planned DSS will allow for the *in-silico* simulation of different treatment options for each of the conditions targeted by EurValve, AS and MR, and thus enable comparison of their immediate haemodynamic outcomes. The anatomy of the valve is determined from medical image data, and this is represented in a three-dimensional (3D) model. The flow through the valve, and the resulting pressure gradients and physiological sequelae, are determined by the complex interaction of the heart, the valve, and the afterload presented by the circulation, as well as by predisposition associated with the genetic profile of the individual. The components of the heart and of the circulation that are not described explicitly in 3D are represented by zero-dimensional (lumped parameter, time variant) or one-dimensional models as appropriate. At a high conceptual level, the envisaged workflow can be described as follows:

- The patient geometry is determined from a patient-individual medical image.
- Simulation input parameters are determined from the electronic health record, from pervasive monitoring, from population data, from literature data, from the patient geometry, from machine learning or from biopsy samples.
- Then, the flow simulation can run according to a certain analysis protocol.
    - The concept behind the 0D model is to provide an initial simulation model with lower accuracy but in significantly less time, that will be quickly developed by partners and that could be integrated within a short time period.
    - The 0D model describes the circulation in the left heart and the systemic circulation. It consists of the heart represented by 2 heart chambers, the mitral and aortic valves.
    - The minimal 0D model will nevertheless be composed of both the pressure and the flow simulation, including time-series data for both models.

3.1.6.2 Technical issues

The inner modelling operations will be directly integrated into EndoSize®. No ROM service or ANSYS Fluent is required for 0D model, where each mathematical equation can be directly implemented into the software framework.

3.1.6.3 Graphical interface

The results will be presented in two views, a pressure model with different adjustable parameters (e.g. ejection fraction), and a flow model. The results will be viewable across the cardiac cycle using a slider-operated adjustable time-setting system that will control a near real-time "live" calculator to simulate the patient at rest and under exercise, both pre and post treatment.

3.1.6.4 Interactions with other WP

WP3, particularly T3.3 will provide the flow simulation models, which do not depend on T3.6, the Reduced-Order Model.

3.1.7 Numerical simulation – 3D model

3.1.7.1 Feature/concept

This is the key concept of EurValve, in which a complete 3D model of the physiological envelope is simulated, to represent the current physiological state of the valve. The challenge is to tune this model using the heterogeneous data that is available for the patient so that it is able to evaluate the effects of the patient's disease state under a range of patient activities. It is important that the DSS is able to operate in timescales that are appropriate to support the clinical process so, instead of the whole highly complex model being operated, T3.6 will develop a Reduced Order Model (ROM) that offers the potential for near real-time diagnostic and prognostic haemodynamics and physiological characterisation. All the results of the ROM task will be used by the DSS tool.

3.1.7.2 Technical issues

While large-scale computing itself is an entirely off-line activity that underpins the development of the models and of reduced-order approximations for clinical operation, the 3D analysis workflow and the dedicated ROM will be directly integrated into the DSS tool to be able to process cases directly through the interface. Access to the ROM facilities will make use of ANSYS Fluent, the executable for which will be installed on the user local machine.

3.1.7.3 Graphical interface

A single-click process will initiate the controllable display of the entire 3D analytical output, with the option to show different components separately using a synchronised timeline.

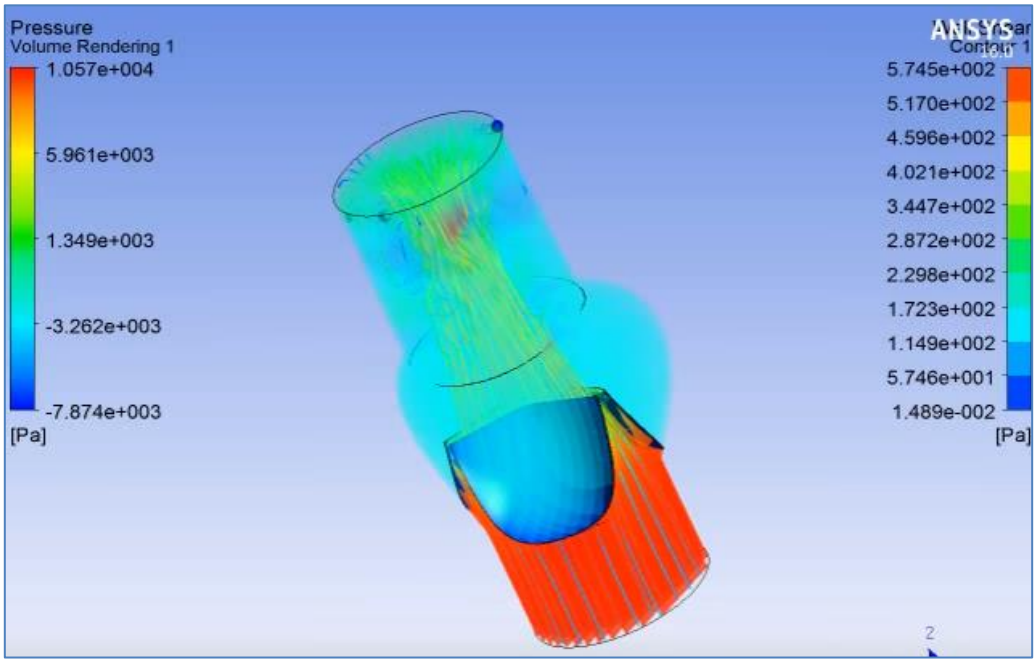

Figure 14: Example of aortic valve fluid simulation. Source: ANSYS

3.1.7.4 Interactions with other WP

WP3 will be the source of the systems required for this feature: T3.3 will provide the flow simulation models, and T3.6 will provide the ROM mechanism.

3.2 Workflow Integration

The success of the DSS depends substantially on the effective integration of recommendations from the EurValve clinical teams (55), and understanding the clinician's workflow, particularly when designing patient-specific applications, is essential to optimal success (10). How to integrate the DSS within the clinician's workflow, however, remains a challenge, in part because there are no current standards for such workflows. A general consensus is that the most effective way to present the proposed type of information is immediately at the point of care, at the time and place of decision making. The information from the DSS can be presented automatically to the clinician or "on demand" (i.e., when the clinician chooses to access the information), one of reasons behind the decision to integrate the DSS within the EndoSize® workflow at the end of the anatomical measurement step (Fig 8b), and before the reporting step (Fig 8c). At that time of interventional planning, the clinician may have some queries about the intervention strategy to be followed, and this positioning seems to fit the workflow most effectively. Anatomical measurements will therefore be directly completed and only clinical parameters will require manual user entry.

3.3 Clinical Consultation

The role of WP6, and particularly Task 6.3, is to apply the DSS to the identified cohort of clinical cases. Considering the current timeline for patient inclusion and that for the beta-version of the DSS, the cohort will be analysed retrospectively with the DSS. As soon as a beta-version of the DSS is released, the software tool will be installed in clinical centres, to test ease-of-use, effectiveness and clinical utility, though it is an open question whether initial deployment in a single centre would offer additional benefit. WP6 will provide information relevant to the use of the DSS in the management of heart valve patients and, because each release of the DSS tool will bring change, interview meetings with the participating clinicians will continue to be conducted. Strong interactions between WP5 and WP6 will be needed to adjust and optimise the user interface, gathering feedback from clinicians to facilitate continuous improvement to both functionality and ergonomy.

3.4 Dissemination

Dissemination of evaluations of commercial DSS systems in community settings is also important for presenting the full picture of DSS design, implementation, and impact. At each internal release of the DSS tool, Therenva will alert stakeholders from WP7, to be able to communicate efficiently. In particular, short videos as well as representative screenshots of the software will be created to present new features throughout the project.

3.5 Minimum Viable Product

The concept of a minimum viable product was introduced in D3.1, and refers to the assembly of primitive components from each subtask of WP3 in order to build a system mock-up as early as PM09. This set of tools, even in their initial versions, could give insights into the underlying infrastructure and allow assessment of the complexity of each tool separately. The process should also provide guidance on potential data connection and computer capability issues. Based on these results, WP5 will have a better view of the integration process and will be able to provide an early mock-up of the graphical interface that will eventually drive the clinical solution.

4 ILLUSTRATIVE INTERFACE

For best practice on DSS design and implementation, multiple publications have been examined (10,56). Enabling all DSS concepts to fit on a single screen requires substantial condensation and simplification, but currently seems to be an important factor in convincing clinicians to engage. The literature reports the overall experience that the likelihood of success in implementing a computerised guideline is inversely proportional to the number of data elements needed. Where a large variety of measures and concepts are present, the DSS tool should be as user-friendly as possible, and speed is generally the parameter that users value most, but if system access is too difficult or time-consuming, potential users may choose to reject the DSS without a proper technical evaluation.

The first decision towards easy access is the integration of the DSS directly into the EndoSize® workflow (section 3.2). Thereafter, Fig. 13 shows a proposition for a system mock-up, with all concepts exposed in a single page. The objective of this interface is to remove the idea of a fixed or preferred operational sequence and provide the user with easy access to each of the concepts described above. All input data will be shown on the left of the interface, by category (anatomical, demographic, co-morbidities), while to the right each of the concepts will be made available through an illustrative image. This early concept for DSS appearance is subject to major change throughout the project's life.

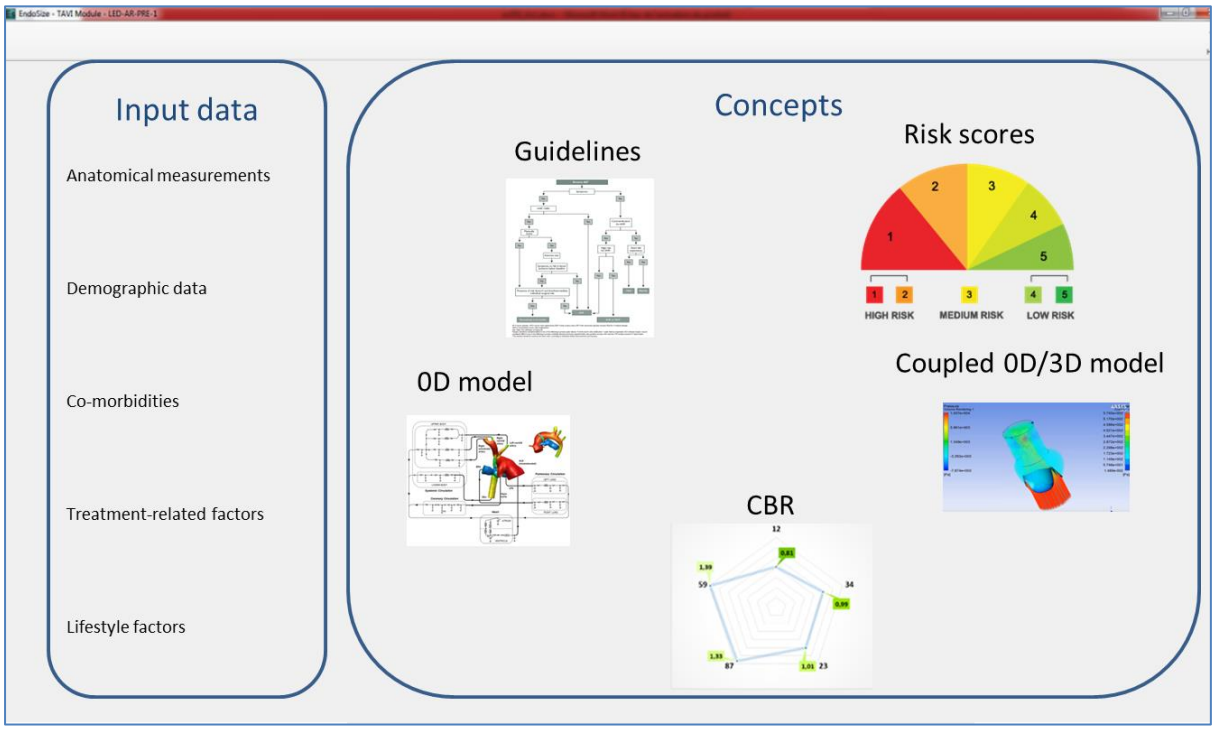

Figure 15: Mock-up of the DSS with all concepts

5 DEVELOPMENT TIMETABLE

The formal EurValve documentation describes two major releases of the DSS tool, to which have been added three internal releases - the first of which is a an early functional assessment to which WP5 will contribute a graphical interface.

The first documented release (the beta version) is due at PM21 (D5.2, D5.3), but production will be advanced to provide a system for review at PM18. This beta version will include facilities for literature data, risk scores, the ECS guidelines, the basic 0D model and the beta CBR module with limited input data.

The second documented release (the final in-clinic version) of the DSS is due at PM30, and will include responses to user experiences. This final version will provide an extended set of patient data on which additional rules will operate. In addition to the concepts from the beta release, it will include the complex 3D models and the final CBR module. The development timetable is presented on Table 3.

When	Deliverable	What
PM9	Minimum viable product	✓ Advanced mock-up of the interface
PM12	Internal release	✓ Risk scores ✓ ECS guidelines
PM18	Beta release - D5.2, D5.3	✓ 0D CFD model ✓ Beta CBR module ✓ Literature data
PM24	Internal release	✓ Final CBR module
PM30	Final release (in-clinic version) - D5.4	✓ 3D CFD model

Table 3: Development Timetable

6 SUSTAINABILITY & EXPLOITATION

Mindful of EurValve's intention to build a decision support system capable of operating in a research environment, whilst also being as close as realistically possible to a market-ready simulation-based standalone system, the DSS tool described herein has been designed both to interface with the EurValve infrastructure and to be capable of independent operation when required.

In concrete terms, all measures and concepts will be directly implemented into the WP5 DSS framework, including 0D and 3D + ROM CFD simulations and the CBR. A facility will be created to permit operation with either an infrastructure-based or a local database with adequate parametric support for CBR and case processing. Similarly the ability to access WP3's segmentation systems will be supported by a facility to work with an equivalent internal mechanism. Post-project sustainability and DSS exploitation will therefore already be comprehensively supported, with the prospect that clinicians will be able to use the upgraded EndoSize® with either a comprehensive pan-European database or, where this is not viable, with their own local light database.

In conclusion, the EurValve consortium will develop a DSS that, although dedicated to a specific domain, will be constructed according to rational principles of re-usability, modularity and ease of maintenance. Consequently, it will serve as a flagship for the general principle of model-based DSS operation, exploiting heterogeneous data across the chosen clinical domain.

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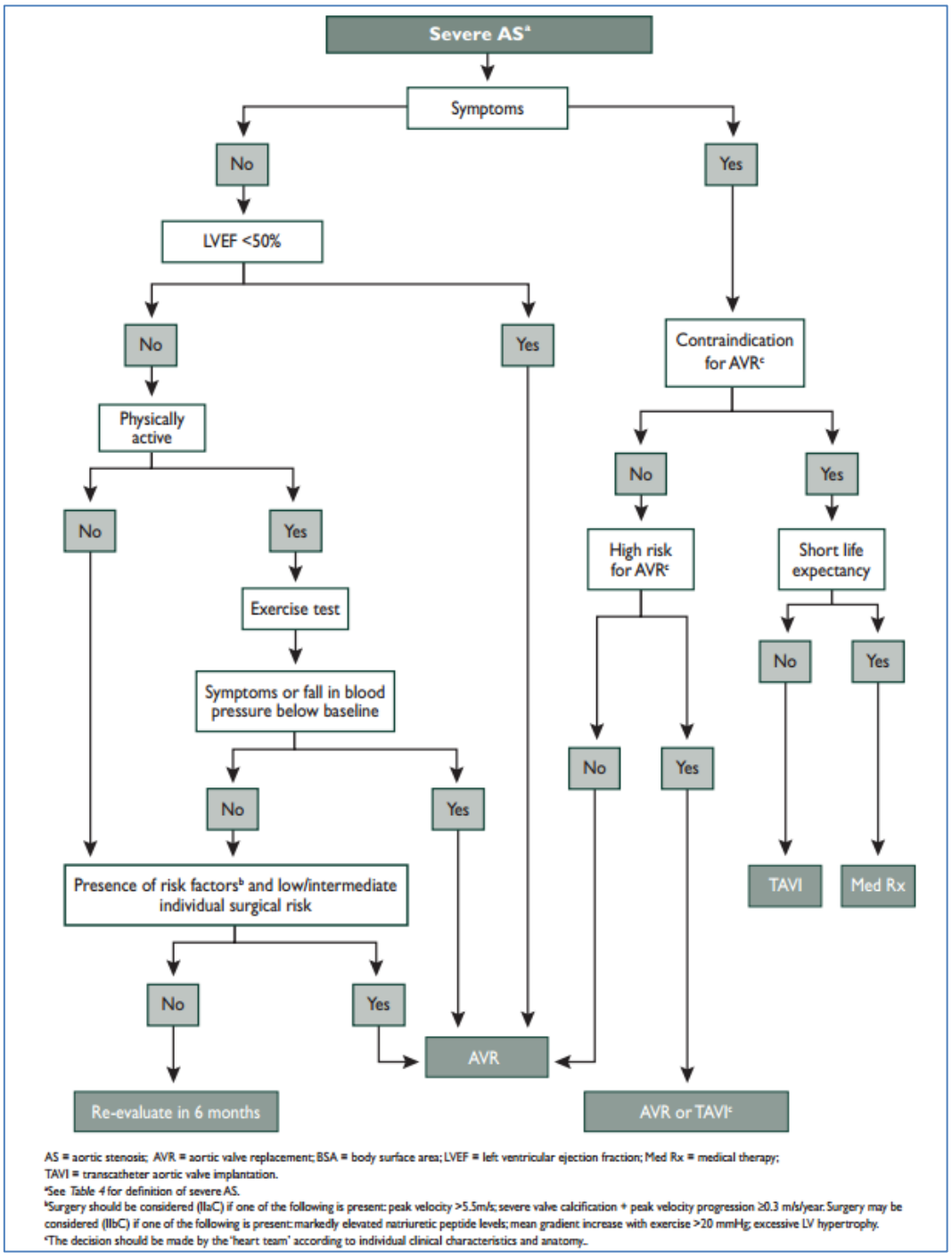
List of Key Words/Abbreviations

AF	Atrial fibrillation
AS	Aortic stenosis
AVR	Aortic valve replacement
BSA	Body surface area
CDSS	Clinical decision support system
CFD	Computational fluid dynamics
DSS	Decision support system
ED	End diastole
EF	Ejection fraction
ES	End systole
EVAR	Endovascular aneurysm repair
FEVAR	Fenestrated endovascular aneurysm repair
FU	Follow-up
ITK	Insight toolkit
LA	Left atrium
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
MR	Mitral regurgitation
MVP	Minimum viable product
PACS	Picture archiving and communication system
SPAP	Systolic pulmonary arterial pressure
STS	Society of thoracic surgeons' risk score
TAVI	Transcatheter aortic valve implantation
TEVAR	Thoracic endovascular aneurysm repair
VHD	Valvular heart disease
VTE	Venous thromboembolism
VTK	Visualisation toolkit

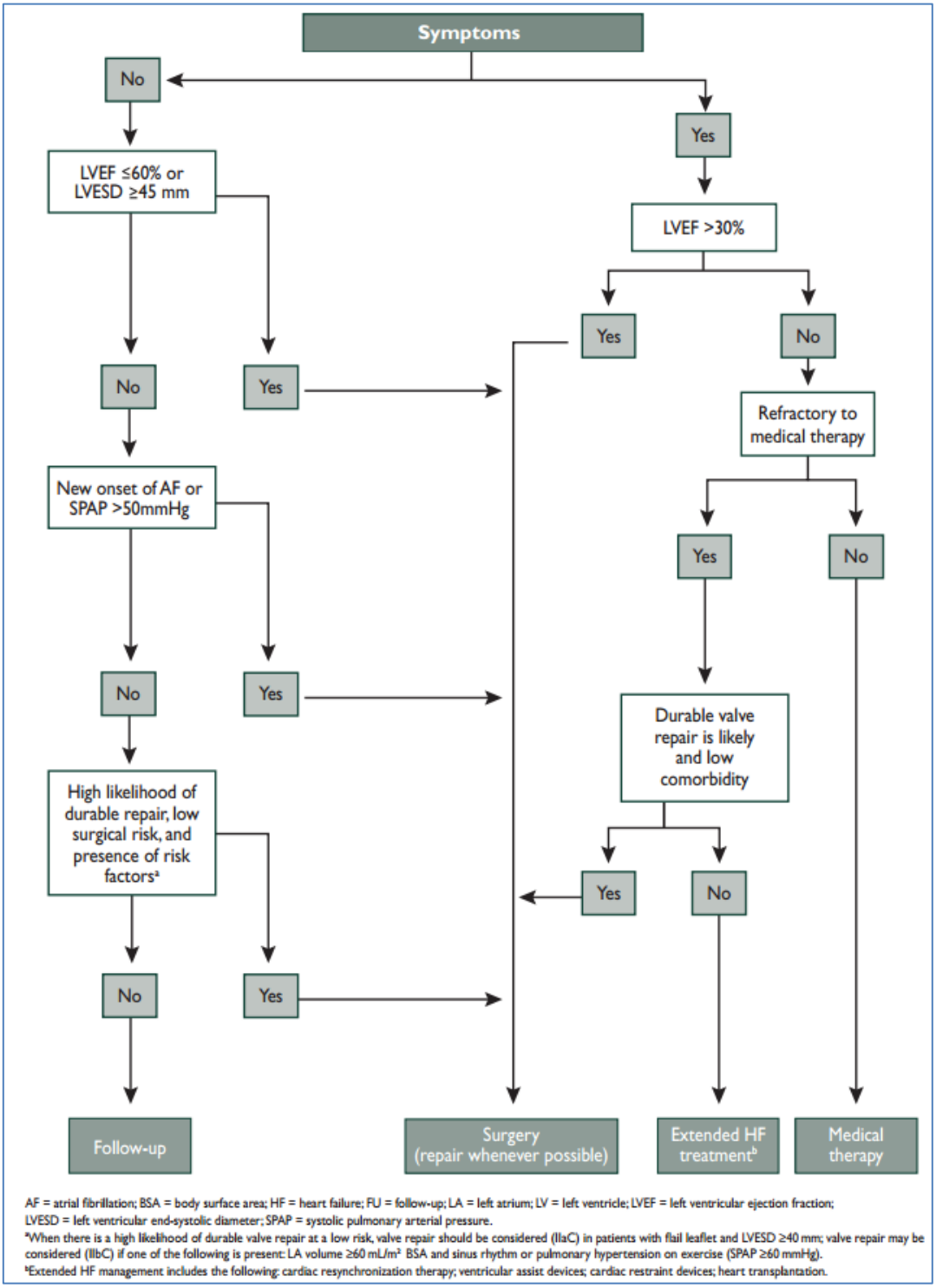
ANNEX 1: ENDOSIZE® USER STORIES

DSS User stories	DSS version
DSS-1: As a user, I can compute relevant anatomical measurement for the aortic valve based on CT	PM30
DSS-2: As a user, I can compute relevant anatomical measurement for the mitral valve based on CT	PM30
DSS-3: The DSS plug-in shall be accessible after the measurement step in EndoSize®	PM12
DSS-4: The set of input parameters are accessible via a form in the DSS tool	PM12
DSS-5: All anatomical measurements computed during the sizing step are automatically filled in	PM18
DSS-6: As a user, I can fill in a form including demographic, co-morbidities, and lifestyle factors for my patient	PM12
DSS-7: As a user, I can re-load all parameters (imaging and clinical) I have previously filled in	PM12
DSS-8: The major concepts shall be accessible through the main DSS graphical interface	PM09
DSS-9: As a user, I want to have access to hyperlinks of relevant literature papers	PM18
DSS-10: As a user, I want to have access to documents of the relevant literature papers	PM18
DSS-11: As a user, I want to have access to the ECS guidelines for aortic stenosis	PM18
DSS-12: As a user, I want to have access to the ECS guidelines for mitral regurgitation	PM18
DSS-13: As a user, I want to be able to compute the EuroSCORE	PM18
DSS-14: As a user, I want to be able to compute the STS score	PM18
DSS-15: As a user, I can use predictive models of post-intervention events based on the set of input parameters	PM30
DSS-16: As a user, I can visualise the 0D model of the aortic and mitral valve, and play with the different time-point	PM18
DSS-17: As a user, I can visualise the entire 3D model of the aortic and mitral valve based on ROM technique	PM30
DSS-18: As a user, I can retrieve the most similar case from the learning database, and have access to its corresponding outcome	PM24
DSS-19: As a user, I can add the current patient to the CBR local database	PM24
DSS-20: As a user, I can remove a case from the local database	PM24

ANNEX 2: ECS GUIDELINES



Annex 2-A: ECS guidelines for AS



AF = atrial fibrillation; BSA = body surface area; HF = heart failure; FU = follow-up; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SPAP = systolic pulmonary arterial pressure.
[a]When there is a high likelihood of durable valve repair at a low risk, valve repair should be considered (IIaC) in patients with flail leaflet and LVESD ≥40 mm; valve repair may be considered (IIbC) if one of the following is present: LA volume ≥60 mL/m² BSA and sinus rhythm or pulmonary hypertension on exercise (SPAP ≥60 mmHg).
[b]Extended HF management includes the following: cardiac resynchronization therapy; ventricular assist devices; cardiac restraint devices; heart transplantation.

Annex 2-B: ECS guidelines for MR

ANNEX 3: COMPUTATIONAL MEASURES AND CONCEPTS

Table 10: Computational measures and concepts

Field Label	Field Name	Data Type	Code/Unit/Comment
Maximum LV Elastance	com_elvmax	Double	[mmHg/ml]
Minimum LV Elastance	com_elvmin	Double	[mmHg/ml]
LV Elastance Offset parameters	com_elvoff	OrderedMap < Double>	[p0 mmHg, V0 ml]
LV Elastance timing parameters	com_elvtimepar	OrderedMap < Double>	[Dimensionless, fraction]
Maximum Left Atrium Elastance	com_elamax	Double	[mmHg/ml]
Minimum Left Atrium Elastance	com_elamin	Double	[mmHg/ml]
Left Atrium Elastance timing parameters	com_elatimepar	OrderedMap < Double>	[Dimensionless, fraction]
Aortic Flow/dP characterisation	com_aQdP	OrderedMap < Double>	[Q l/min, dP mmHg]
Aortic Flow/dP characterisation coefficients	Com_aQdPcoeff	OrderedMap < Double>	[mixed]
Mitral Flow/dP characterisation	com_mQdP	OrderedMap < Double>	[Q l/min, dP mmHg]
Mitral Flow/dP characterisation coefficients	Com_mQdPcoeff	OrderedMap < Double>	[mixed]
Total Blood Volume	com_tbv	Integer	[ml]
Heart Rate	com_hr	Integer	[beats/minute]
Systemic resistance proximal	com_sysresprox	Double	[mmHg/ml]
Systemic resistance distal	com_sysresdis	Double	[mmHg/ml]
Systemic compliance	com_sysresdis	Double	[ml/mmHg]
Systemic Oxygen Consumption	com_O2_rate	Double	[ml/min]
Left ventricle volume at ED	com_lvved	Integer	[mL]
Left ventricle volume at ES	com_lvves	Integer	[mL]
Volume curve left ventricle	com_vc_lv	OrderedMap <Integer,Double>	{*TimePoint*, *Measurement*}
Left ventricle Ejection fraction	com_lvef	Integer	[%]
Cardiac output	com_co	Integer	[mL/min]
Barocontrol afferent signal parameters	com_baro_cp	OrderedMap <Double>	*{fmin [s^{-1}], fmax [s^{-1}], Pn [mmHg], kn [mmHg]}*
Barocontrol efferent sympathetic signal parameters	com_baro_es	OrderedMap <Double>	*{fes0 [s^{-1}], fesinf [s^{-1}], kes [s]}*