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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP5 Strand B:

Post-launch evidence generation (PLEG) and registries

EUnetHTA WP5B PLEG Pilot on Left Ventricular Assist Device (LVAD) for destination therapy

Minimum data set report

April 2021

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Conflicts of interest

All participants involved in the production of this pilot have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA declaration of interest and confidentiality undertaking form.

Stakeholder involvement

The company in charge of the development of the product has been contacted at the beginning of the pilot and was kept informed about different pilot steps and outputs. No other stakeholders have been involved at pilot level at the stage of the production of this report.

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List of abbreviations

ADHF	*Advanced heart failure*
BTT	*Bridge to transplantation*
COS	*Core Outcome Set*
DT	*Destination therapy*
EACTS	*European Association for Cardio-thoracic Surgery*
EQ-5D	*EuroQol-5 Dimensions*
ESC	*European Society of Cardiology*
EU	*European Union*
EUnetHTA	*European Network of Health Technology Assessment*
HTA	*Health Technology Assessment*
HF	*Heart failure*
JA	*Joint action*
KCCQ	*Kansas City Cardiomyopathy Questionnaire*
KCE	*Belgian Health Care Knowledge Centre*
LVAD	*Left ventricular assist device*
OMM	*Optimum medical management*
PICO	*Population, intervention, comparator and outcome*
PLEG	*Post-launch evidence generation*
QALY	*Quality-adjusted life year*
RCT	*Randomised clinical trial*
RWD	*Real-world data*
UK	*United Kingdom*
LV	*Left ventricle*
WP	*Work package*

1. SYNOPSIS

The European Health Technology Assessment Network (EUnetHTA) WP5B1 is currently testing the possibilities of collaborating in the development of quality registry data for health technology assessment (HTA) purposes. Within this work package (WP), we are conducting a pilot study facilitating cross-border collaboration for real-world data (RWD) exchange. The pilot focuses on the use of a left ventricular assist device (LVAD) as destination therapy (DT). Its main objective is to test collaboration of member states in the definition of a "minimum data set" with the purpose of sharing registry data on technologies that have key uncertainties at the time of the HTA assessment. This pilot will help to answer the gaps and uncertainties found by learning how LVADs are actually used and how they work in real-world practice rather than in clinical trials.

The present report corresponds to step five of the pilot, which consists of agreeing on the common data set for RWD collection for this product and specifying research methods.

For more details on the pilot and its different steps, please see the Common Evidence Gaps report insert link to the report web page.

2. STUDY BACKGROUND

2.1 EUnetHTA WP5 Strand B

The primary objective of WP5 strand B pilots is to explore the collaboration on post-launch evidence generation (PLEG) and enhance the use of high-quality registries in HTA.

Enhance the use of high-quality registries in HTA:

- In PLEG pilots using data from registries, focus on linking data from registries in a number of countries and learning from experience.
- Adapt existing quality standards for registries (e.g. PARENT guidelines) to HTA needs and develop a practical tool (Standards Tool for Registers in HTA) to enable registry owners and developers to apply standards consistently and transparently to promote cooperation on the collection and use of registry data between countries.
- The target groups for this tool are both registry owners (including clinicians, industry and academics) and HTA bodies.
- Develop a tool to support permanent collaboration on PLEG, based on the lessons learned from the pilots, and overall results and conclusions of Strand B activities.

The Scientific Advice Unit, avalia-t, Galician Agency for Health Knowledge Management, ACIS (Spain) and the National Institute for Health and Care Excellence (NICE) are leading this project with the collaboration of the Belgian Health Care Knowledge Centre (KCE) and Agenzia Nazionale per i Servizi Sanitari Regionali, Italy (Agenas).

2.2 PLEG Pilot on LVAD for DT

LVADs are used as circulatory support to help the damaged left ventricle (LV) in patients with end-stage heart failure (HF). Sometimes, LVAD implantation is the main option for patients with end-stage HF who do not meet the criteria for receiving a heart transplant, known as destination therapy (DT).

The overall benefits are deemed to outweigh the risks if LVADs are used in appropriately selected patients, but important uncertainties remain regarding the use and long-term outcomes in real practice settings as well as the criteria for establishing which patients would most benefit from these devices. These uncertainties and other challenges related to the organisation of services and patient management can clearly undermine the optimal use and cost-effectiveness of these devices, given their high cost. The collection of real-world prospective data could provide information to resolve these key uncertainties and improve the quality of care provided.

Gathering this data at a European level would allow us to compare outcomes from different countries, which would make the conclusions more robust and increase the applicability of registry results.

2.2.1 The disease and available treatments

HF is a highly prevalent disease that increases significantly the expenditure of the health care systems. The prevalence of HF in Europe is estimated to be around 2–3% of the general population, of which 0.4% have advanced HF (ADHF).

When the HF is advanced, pharmacological and dietary treatment are no longer effective and patients experience severe symptoms despite appropriate medical therapy. These cases require ADHF treatments to provide support to the failing heart. These can include constant intravenous (iv) medications, mechanical circulatory support (partial or total artificial hearts), and heart transplants. Heart transplantation is the only definitive therapy and thus the treatment of choice, although it is limited by organ availability and waiting time until a compatible organ is available. In addition, many patients do not qualify for a heart transplant due to a permanent contraindication to it.

LVADs have been used as a “bridge” to heart transplantation (BTT) option in patients on the waiting list for transplantation but clinically deteriorating before a donor heart is available and has also been proposed as a replacement (destination) therapy for failing hearts in patients who are not candidates for heart transplantation.

In their first generation, LVADs were pulsatile pumps, but the most modern devices (second-generation) are continuous flow pumps. They can be centrifugal or axial flow pumps. Currently, the HeartMate 3™, HeartWare HVAD™ System™, Incor® and Jarvik 2000 are the only approved devices for DT in the European Union (EU).

Major complications associated with LVADs include bleeding, infection, and device malfunction. Temporary right ventricular failure immediately following an LVAD placement can occur in a significant number of patients requiring inotropes or a right ventricular assist device. According to the European Society of Cardiology (ESC) Guideline (2016), patients who are candidates for LVAD implantation should not present a severe deterioration in right ventricular function together with severe tricuspid regurgitation. Moreover, factors such as obesity or cachexia (BMI <20 kg/m^2 in people <65 years and <22 kg/m^2 in people >65 years) are both associated with an increased risk of infections, right ventricular dysfunction and history of gastrointestinal bleeding [1,2].

These devices are complex and therefore a careful evaluation should be carried out to assess all baseline factors before LVAD implantation. Clinical expert consensus documents pointed out the most important are cardiac/anatomical factors, non-cardiac factors such as age, comorbidities that determine hope or quality of life, psychiatric (ability to handle the device) and social (family support) aspects, as well as the assessment of surgical risk associated with LVAD implantation as target therapy using specific scales such as the HeartMate II Risk Score [3,4]. The specific contribution of these factors to the overall results is relatively unknown.

2.2.2 HTA and reimbursement status of LVAD

The reimbursement of LVADs is a matter of debate in many EU countries, being in some only indicated for temporary support while patients await transplant or recovery. In Spain, LVADs are included in the national health system common services, with the following indications:

- as a bridge to heart transplantation,
- as a bridge to the recovery in patients with acute HF,
- and as a DT (permanent or long-term) for patients who are not candidates for heart transplantation.

2.2.3 Summary of the safety and effectiveness evidence

Three national HTA reports have been published on this topic (only summaries in English). The latest was published in May 2018 (https://avalia-t.sergas.gal/DXerais/765/avalia-t201702DAVI.pdf). It has been

requested by the Commission on Benefits, Insurance and Financing (Spanish National Health System), with the aim of re-evaluating the evidence regarding the clinical effectiveness and safety of LVADs as destination therapy, as well as analysing the costs and the organisational, ethical, social and legal aspects that may condition their effective implementation in the Spanish National Health System [5].

The bibliographic search identified a HTA report from the Health Quality Ontario HTA agency (Canada). This was updated and its aim extended, obtaining eight original studies, six that evaluated safety and/or effectiveness (one ENDURANCE randomised clinical trial, and five observational studies), two cost-effectiveness studies, three qualitative studies on patient/carer acceptability, and seven studies that analysed the ethical impact. The quality of the evidence was classified as moderate to very low, according to the GRADE system.

In randomised clinical trials with an LVAD as a DT (REMATCH and ROADMAP) it has been found that patients treated with a continuous or pulsatile-flow LVAD achieved a higher 1-, 2-, and 4-year survival rate, better quality of life, and better functional status in comparison with the optimal medical treatment. The continuous-flow LVAD presented a lower frequency of right heart failure, respiratory dysfunction, device-related infection and sepsis than the pulsatile-flow LVAD. However, the continuous-flow LVAD presented a thrombosis rate of 4%, compared with no cases with the pulsatile-flow LVAD. The continuous-flow LVAD increased the 1- and 2-year survival rate, and improved functional status in comparison with the pulsatile-flow LVAD, although finally the quality of life of patients treated with either of the two versions was similar. The ENDURANCE trial found that patients treated with the HeartWare™ LVAD system had a higher frequency of stroke in comparison with the HeartMate® II, although the survival rate for both groups was similar. The studies that assessed patient and/or carer acceptability indicated in some cases, the important burden of treatment with LVAD as a DT, while others highlighted the opportunity the device has offered them to improve their quality of life.

With regards to the implementation of an LVAD as a DT, it is important to note the incremental cost-effectiveness ratio, which is higher than 100,000 Euro/quality-adjusted life years (QALYs) (107,000–187,000 Euro), in addition to its organisational impact (i.e. presence of a multidisciplinary team with adequate and continuous training, education for patients and/or caregivers, adaptation of patient's homes and coordination of the different health care settings).

Finally, the ethical aspects associated with the use of an LVAD as a DT are focused on offering the patient and/or caregiver the different therapeutic options that are available through a specially designed informed consent form for end-of-life clinical situations.

2.2.4 Description of on-going studies

Four on-going studies were identified:

- Evaluation of the Jarvik 2000 Left Ventricular Assist System with Post-Auricular Connector-Destination Therapy Study. An open-label randomised clinical trial (RCT) the aim of which is to assess the safety (serious adverse events) and efficacy (event-free survival such as device replacement/repair or stroke with a modified Rankin scale score >3) of the Jarvik 2000 LVAD as target therapy compared with the HeartMate II® in 350 patients with ADHF who are not candidates for heart transplantation.

- Apogee International. A prospective, non-interventional, post-market, multi-site registry which aim is to confirm safety and efficacy of the HVAD™ System when used as intended, in "real world" clinical practice and to enhance scientific understanding of the implant procedure in patients receiving a HeartWare™ HVAD™ for BTT and DT indications. It is estimated to include 300 patients intended to be implanted with a HeartWare™ device per the current (local) guidelines.

- Apogee, a HeartWare™ HVAD™ Destination Product Surveillance Registry (PSR) Platform. A prospective, observational, post-market, on-label, multi-site study in 200 patients with chronic HF, the aim of which is to enhance scientific understanding of the implant procedure, optimised blood

pressure management, and anticoagulation/ antiplatelet therapy in patients receiving a Medtronic HeartWare™ Ventricular Assist Device (HVAD™ System) for destination therapy.

- Destination Therapy Post Approval Study (DT PAS). A prospective, observational, multi-site study, the aim of which is to further confirm safety and effectiveness of the HeartWare™ Ventricular Assist Device System (HVAD™ System) when used as intended, in real-world clinical practice in 300 patients intended to be implanted with a HVAD for use as DT.

3. RATIONALE OF THE STUDY

The main uncertainties identified in the 2018 avalia-t report [5] relate to safety and to the eligibility criteria for the appropriate selection of the best candidates for LVADs as destination therapy (patients who would obtain the best outcomes in relation to their comorbidities or previous interventions/clinical history).

Information is lacking regarding the baseline patient characteristics and technical factors that could predispose to severe adverse events and early mortality, raising important doubts regarding the optimal use of these devices.

Important gaps have also been identified in relation to the durability of the LVADs and the long-term management (device replacement and hospital readmissions management) of these patients. This information is essential to estimate the organisational and total cost impact of these devices (due to implantation, replacement or removal of the device).

Based on the conclusions it was recommended that it would be appropriate to set up a national post-introduction observational registry to follow up on the use and outcomes of the LVADs used as a DT. Furthermore, it would help to know the economic and organisational impact of the use of LVADs as a DT in routine clinical practice. Finally, adverse events seem to differ according to the mechanism of action, so it would be appropriate to compare the different available devices.

This pilot will help to answer the gaps and uncertainties described before, by learning how the LVAD is actually used and how it works in real-world practice rather than in clinical trials.

A North American mandatory registry (Interagency Registry for Mechanically Assisted Circulatory Support-INTERMACS) is collecting data on LVADs as DT since 2006. However, due to the differences between the European and American health systems, conclusions from this registry may not be applicable to our setting. In this sense, the EUROMACS registry was created in 2009 with the goal of gathering European data on mechanical support systems. This registry, whilst comprising a great number of members, is limited by the fact that it does not exert a strict follow-up control, being voluntary in nature, and does not allow for direct comparisons due to the differences in reporting and applied definitions.

Collaboration between Member States in the definition of the minimum core data set is important to obtain a quality record. This information will have the potential to support the decision-making process for pricing and reimbursement and to elaborate recommendations regarding appropriate use.

- The main objectives of this study are:
    - To define a minimum core data set for the registry of patients with LVADs as DT.
    - To generate a quality dataset of patients with LVADs as DT.
    - To develop evidence that would be suitable to support decision-making.
    - To assess possible levels of cross-border collaboration on RWD generation and exchange.

4. RESEARCH QUESTION

The research question of the pilot of LVAD was elaborated following the JA2 Position paper on how to best formulate research recommendations[1] (Table 1).

Table 1. Evidence profile of LVAD as destination therapy

Evidence profile of the technology	
Topic and rationale	
Title of the assessment	Pilot on Left Ventricular Assist Device (LVAD) for destination therapy
Research question	Patients: Patients with end-stage heart failure (HF) who are candidates for LVAD implantation and who also do not meet the criteria for receiving a heart transplantation such as age and/or co-morbidities (known as destination therapy [DT]) Intervention: LVAD as DT Outcomes: The outcomes will include patient characteristics and device specific information: safety related outcomes, effectiveness related outcomes, economic related outcomes and other organisational, social or ethical aspects.
Rationale	This pilot will help to answer the gaps and uncertainties described before by learning how the LVAD is actually used and how it works in real-world practice rather than in clinical trials. A North American mandatory registry (Interagency Registry for Mechanically Assisted Circulatory Support – INTERMACS) is collecting data of LVADs as destination therapy since 2006. However, due to the differences between the European and American health systems, conclusions from this registry may not be applicable to our setting. In this sense, the EUROMACS registry was created in 2009 with the goal of gathering European data on mechanical support systems. This registry, whilst comprising a great number of members, is limited by the fact that It does not exert a strict follow-up control, being voluntary in nature, and does not allow for direct comparisons due to the differences in reporting and applied definition.
PICO	
Population	Patients with end-stage HF who are not candidates for heart transplantation due to some clinical condition that contraindicates it (fragility, obesity, pulmonary hypertension, recent malignant tumour, etc.) or unwilling (for religious or other reasons)
Intervention	LVADs with indication for destination therapy (HeartWare™ HVAD™ System, HeartMate II®, HeartMate 3™, Jarvik 2000 or Incor®)
Comparator(s)	None
The most important/ critical outcomes (based on discussions with	• Safety: adverse events associated with the use of DAVI collected in evidence such as neurological complications (stroke or transient ischaemic attack), right heart failure, respiratory failure, device thrombosis, infection and haemorrhage.
	• Effectiveness: variables that assess the effectiveness of LVAD as DT collected in the evidence for example: hospital mortality, survival, quality of life, patient/caregiver satisfaction, treatment adherence, reintervention, among others.

[1] JA2 Position paper on how to best formulate research recommendations.

clinical experts)	• Economic impact: variables such as the unit cost of the technology, professional fees (including medical, nurses, administrative personal, etc.), consumables and supplies needed in a long-term LVAD programme. Moreover, it should be considered costs of hospital readmission and reintervention due to high rate of adverse events on patients with LVAD.
	▪ Organisational, social, ethical and legal impact.
Study design(s)	▪ Systematic reviews and meta-analysis. ▪ Comparative studies: RCTs, studies of cohorts, cases and controls and series compared with pairing by propensity score-propensity score matching or other techniques case matching statistics. ▪ Prospective observational studies (without control group). ▪ Studies of costs and cost-effectiveness/utility/benefit, etc. ▪ Qualitative studies on patient and/or caregiver perspectives and organisational impact, social, ethical or legal derived from the use of LVADs as DT.

As presented in the Common Evidence Gaps report insert link to the report web page, most team members identified a need for further research. Different outcomes, i.e. safety, effectiveness, satisfaction of patients/ caregivers and cost-effectiveness/budget impact related to the use of LVADs as DT were considered to be subject to uncertainties on national HTA reports. Below is a summary of the main evidence gaps:

- Information is lacking regarding the baseline patient characteristics and technical factors that could predispose to severe adverse events and early mortality, raising important doubts regarding the optimal use of these devices.
- The survival in the longer term is unknown, as well as the durability of the devices or the need for a replacement beyond 2 years. Moreover, a common definition of event-free survival would be important for future LVAD-DT studies or registries.
- The long-term functional status and the progression or recurrence of the target disease is another of the uncertainties raised by the evaluation agencies.
- The degree of rehospitalisation is another doubtful aspect to be considered due to its influence on the quality of life and the economic impact that entails.
- The quality of life (assessed by instruments such as the Minnesota Living with Heart Failure questionnaire, the Kansas City Cardiomyopathy Questionnaire [KCCQ], the EuroQol-5 Dimensions [EQ-5D] or Short Form-36 test) is generally measured at 1-year post-implant, but it is unknown in the longer term.
- Treatment with an LVAD as a DT must be offered through a specially designed informed consent form for end-of-life clinical situations.
- The cost data concerning LVAD as DT are limited.

The research recommendations arising from the evidence gaps were developed in collaboration with pilot team members. These research recommendations reported according to the PICO (population, intervention, comparator and outcome) scheme are reported in detail in the Common Evidence Gaps report insert link to the report web page.

In summary, members of HTA bodies agree that further robust studies with standardised data collection are needed and thus properly maintained and audited mandatory registries may be the solution.

The following section dealing with the definition of research methods and study outcomes (common data set) specifies the parameters to be analysed in the real-world setting.

5. RESEARCH METHODS

5.1 Study design

Both published and ongoing studies show several evidence gaps with regards to the effectiveness and safety of these devices. In addition, doubts remain regarding the patients that would most benefit from these devices or the potential differences between available devices. These data are relevant to ascertain the best treatment option in real clinical practice. Moreover, an estimation of organisational and economic impact due to long-term use of LVADs is considered necessary in order to analyse barriers and facilitators in the process of implementing a long-term ventricular assist program in a health care system.

The PLEG Pilot of LVAD is a prospective observational study. This real-world prospective registry, being based on a minimum data set developed on common shared gaps, could provide key information to resolve existing uncertainties and improve the quality of care provided in the clinical practice. Moreover, it could help the future gathering and sharing of data at a European level, which would make the conclusions more robust and increase the applicability of registry results. As well, it should be considered of interest at least in some variables for which could be necessary (i.e. organisational/economic impact, hospital readmission, among others) to perform comparative analysis of LVAD vs controls (i.e. patients treated with optimum medical management [OMM]). These would be gathered from medical records (hospital data) or from published studies; or in cases where the former are unavailable, using propensity score matching methods.

The REQueST tool[2] was used to evaluate the quality of PLEG Pilot of LVAD for DT and to identify the potential limitations of the study. The main limitations are related to essential standards of registry; specifically, it does not have a data cleaning plan and an analytical plan for missing data. Regarding additional requirements, the registry protocol was not set up with an ethical committee approval. Nevertheless, ethical expert was involved in its development, in order to ensure research ethical requirements were fulfilled. Moreover, according to clinical registries start-up procedure developed by the Spanish HTA network (RedETS), the ethical committee of the centres that participate in the registry prior to its beginning will review the ethical requirements of the registry.

The consumption data of devices provided by the manufacturers will be checked with the implanted LVAD included in the registry. In order to ensure the quality of the registry, each month it will be important that the outcomes have been filled in correctly. In case any data are missing, they will be requested from the implant LVAD centre.

5.2 Study population

The inclusion and exclusion criteria are detailed bellow. Initially, this selection criterion of patients is based on guidelines elaborated by the ESC [1] and European Association for Cardio-Thoracic Surgery (EACTS) [6]. Afterwards, it was modified according to comments received by clinical experts who participated in the development of protocol of the LVAD registry. The process of patient selection is summarised in Figure 1.

5.2.1 Inclusion criteria

Adult patients with advanced HF (Table 2) who are candidates for LVAD implantation after evaluation by the multidisciplinary committee of the centre and also have clinical situations that prevent cardiac transplantation.

Table 2. Candidate patients for LVAD implantation

Patients with ADHF due to dilated heart disease with LVEF <25% (NYHA IIIB–IV and INTERMACS 2–4) despite the use of medical treatment and/or other devices and meeting at least one of the following criteria:
Inotropic drug dependence

[2] REQueST tool and its vision paper. Available from://eunethta.eu/request-tool-and-its-vision-paper/

Dependence on some short-term mechanical circulatory support
Episodes of decompensated HF (congestion or low output) requiring iv treatment or malignant arrhythmias that have required unscheduled care in the previous 12 months without precipitating cause
Severe impairment of functional class (VO_2 max <12–14 ml/kg/min) of cardiac cause
Progressive target organ dysfunction (renal and/or liver function) due to reduced perfusion and not to inadequate ventricular filling pressure (pulmonary capillary pressure ≥20 mmHg, and systolic blood pressure ≤80–90 mmHg or cardiac index ≤2 L/min/m²

References: Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(11):1505–35. Potapov EV, Antonides C, Crespo-Leiro MG, Combes A, Farber G, Hannan MM, et al. EACTS Expert Consensus on long-term mechanical circulatory support. Eur J Cardiothorac Surg. 2019;56(2):230–70.
Abbreviations: ADHF=advanced heart failure; HF=heart failure; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association.

5.2.2 Exclusion criteria

- Patients with advanced HF who receive an LVAD with an indication other than that of destination therapy.
- Patients with advanced HF with any of the following clinical situations that advise against LVAD implantation (modified from Potapov et al. (2019) [6]):
    - Right ventricular dysfunction
    - Inability to receive chronic treatment with dicoumarin anticoagulants
    - Obesity (BMI ≥35 kg/m²) or cachexia (BMI <20 kg/m² in people <65 years and <22 kg/m² in people >65 years)
    - Untreated mitral stenosis or aortic regurgitation or mechanical aortic prosthesis
    - Active malignant neoplasm with reduced life expectancy (<2 years) evaluated by the Tumour Committee of the LVAD implant centre
    - Active bacterial or fungal infection
    - Irreversible liver or kidney dysfunction
    - Severe lung disease presenting markers of severe or disabling ventilatory dysfunction (i.e. forced expiratory volume (FEV)1 <40% or forced vital capacity (FVC) <50%)
    - Severe atherosclerotic disease (cerebral or peripheral vascular)
    - Insulin-dependent diabetes mellitus with severe end-organ complications
    - Active substance abuse, unwilling to stop abuse
    - Comorbidities that affect the life expectancy or quality of life, neurological or psychiatric diseases that can condition the handling of the device (for example: depression or frailty)
    - Social/family factors that condition proper management of LVAD as a consequence of a lack of support.

5.3 Intervention and comparator

5.3.1 Intervention

LVAD with indication for DT

LVADs act like a pump, generating a circulatory flow (specific depending on the device considered), which allows to partially or totally replace the function of the heart in situations of severe heart failure (acute or chronic), which does not respond to other treatments. The pump is connected to the left ventricle through an inflow and an outflow cannula that connects it to the ascending aorta. Finally, a cable connects the pump to the external console with a microprocessor that controls the operation of the pump and collects information from it. The energy necessary for the operation of the system is supplied either through two batteries, or with a battery and electric current. The storage of system data and the adjustment of parameters of the external console is carried out through a touch screen computer equipped with specific software.

There are various types of devices, which can be classified based on their characteristics. Depending on the duration of ventricular support, they are differentiated into short-term or temporary devices used for hours or days, and long-term or permanent LVADs used as a BTT, recovery, and rarely as DT. Jarvik 2000 and Incor® are devices belong to the second LVAD generation, and HeartWare™ HVAD™ System and HeartMate 3™ belong to the third generation. All of them are devices of continuous flow and lay out Conformitté Européenne (CE) approval for the indication of destination therapy.

LVAD is used in this study in accordance with its approved indication.

5.3.2 Comparator

Patients who are candidate to LVAD as DT but reject it; therefore they would receive OMM.

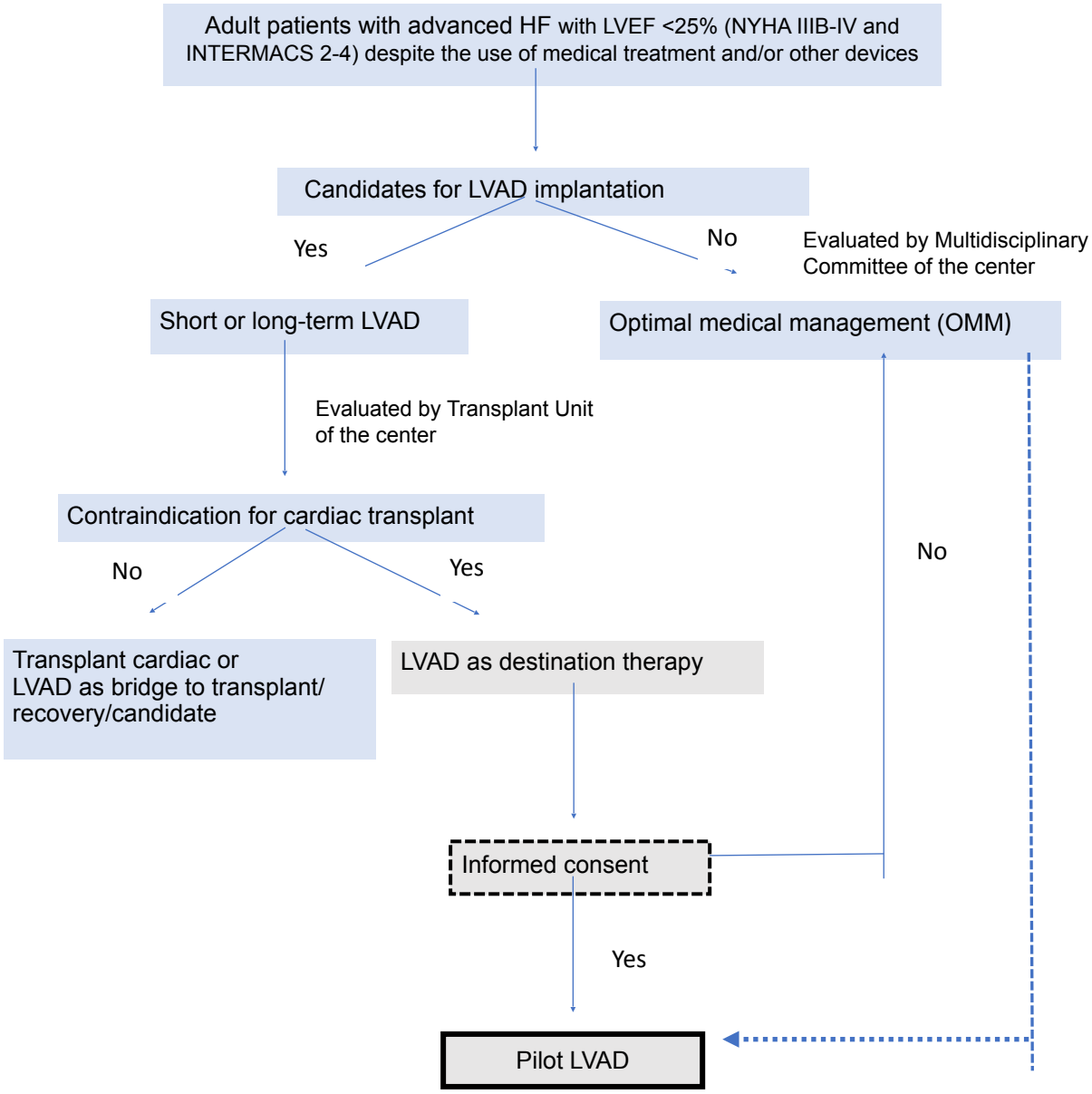

Figure 1. Flow chart of population selection

5.4 Study outcomes and variables to be collected (minimum data set)

5.4.1 Core Outcome Set development

Evidence gaps were based on the four national assessments from the Health Technology Assessment Agencies NICE, KCE, Agenas and Avalia-t. Once the main uncertainties were detected, collaborating

partners were responsible for agreeing on the key outcomes and proposing the preliminary minimum dataset to be registered. Thus, developing a list of candidate domains to be part of the Core Outcome Set (COS). Figure 2 summarises the development process of the COS.

Forty-six key outcomes were agreed by agencies relating to safety (n=21), effectiveness (n= 15), satisfaction and acceptability of the patient (n=2) as well as cost-effectiveness, budget impact and organisational impact (n=8). In addition, 25 stratification factors were proposed. The preliminary minimum data set to be recorded in any LVAD registry account to 69 variables/measures. Of these, 23 refer to baseline patient characteristics and stratification factors.

A two-round Delphi survey with experts was carried out to test the acceptability and feasibility of implementation and to identify additional key outcomes. The survey participants included expert cardiologists from Spain and the United Kingdom. The invitations to participate in the Delphi were sent by email personally to expert cardiologists with experience in the LVAD implantation. Likewise, an invitation was sent to participate through the Spanish Society of Cardiology. To contact patients, we relied on several associations of cardiac patients. Eight expert clinicians participated in the Delphi survey. They all signed the Declaration of Interest and Confidentiality Undertaking (DOICU) form.

The participants marked, among the list of possible domains, which of them they considered important and feasible for the COS or not. Delphi participants rated the importance of each item on a scale from one (not important) to nine (critically important). In round one of the Delphi study, participants could suggest new items to be included in the second round. In round two, each participant who participated in round one was shown the number of respondents and distribution of scores for each item, together with their own score from round one.

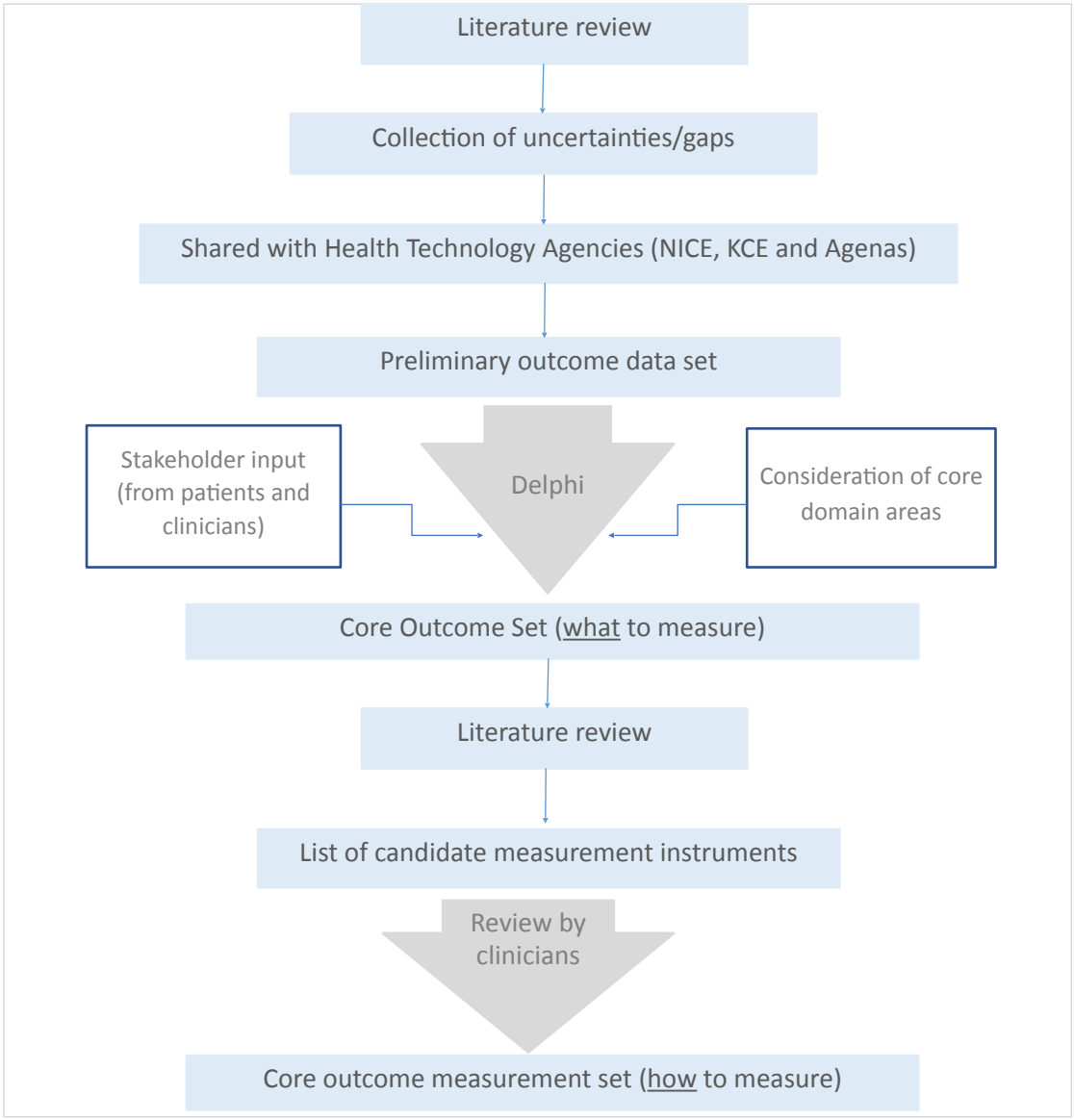

Figure 2. Core Outcome Set development

Once a consensus was reached on the core outcome set, a specific bibliographic review of the literature was carried out to define the measurement instruments, as well as the most appropriate definition for each of these. The clinical expert group reviewed and approved the final measurement set. The proposed core measurement set was reviewed by a series of expert European cardiologists in order to ensure that the definitions were applicable to all countries participating in the project.

The final core outcome measurement set proposal is composed of 15 outcomes and 48 variables/measures (Table 3) divided into three main domains. Annex A displays the specific parameters to be measured for each variable, as well as its definition, reporting source, etc.

Table 3. Core outcome and variable set classified by main domains

Outcome	Variable	Prognostic/stratification factor
Safety		

Outcome	Variable	Prognostic/stratification factor
In-hospital death	• Date of death • Cause of death (if should be collected if CV and non-CV death)	• By device type • By the availability of transplant unit • By baseline characteristics of patients (age, sex, smoking, alcohol, BMI, FEVI, end-diastolic of LV comorbidities, previous cardiac interventions/devices and pharmacological therapies used)
Cardiac adverse events	• Right-sided heart failure • Cardiac arrhythmias • Atrial fibrillation/flutter • Ventricular arrhythmia that required defibrillation	• By device type • By the availability of transplant unit • By baseline characteristics of patients (age, sex, smoking, alcohol, BMI, FEVI, end-diastolic of LV, comorbidities, previous cardiac interventions/devices and pharmacological therapies used)
Neurological adverse events	• Stroke • Transient ischaemic attack	• By device type • By the availability of transplant unit • By baseline characteristics of patients (age, sex, smoking, alcohol, BMI, FEVI, end-diastolic of LV comorbidities, previous cardiac interventions/devices and pharmacological therapies used)
Other serious adverse events	• Renal dysfunction • Respiratory failure • Hepatic dysfunction • Sepsis • Bleeding	Not considered relevant by Delphi expert panel
LVAD device-related adverse event	• Major infection LVAD-related • Pump thrombus • LVAD major failure	• By device type • By the availability of transplant unit • By baseline characteristics of patients (age, sex, smoking, alcohol, BMI, FEVI, end-diastolic of LV comorbidities, previous cardiac interventions/devices and pharmacological therapies used)
Effectiveness		
Overall survival	• Date of surgery • Date of death • Cause of death	• By device type • By the availability of transplant unit • By baseline characteristics of patients (age, sex, smoking, alcohol, BMI, FEVI, end-diastolic of LV comorbidities, previous cardiac interventions/devices and pharmacological therapies used)
Survival free from CV event	• Date of right heart failure • Date of cardiac arrhythmia • Date of atrial fibrillation	Not considered relevant by Delphi expert panel

Outcome	Variable	Prognostic/stratification factor
Survival free from stroke	• Date of surgery • Date of stroke	• By device type • By the availability of transplant unit • By baseline characteristics of patients (age, sex, smoking, alcohol, BMI, FEVI, end-diastolic of LV comorbidities, previous cardiac interventions/devices and pharmacological therapies used)
Survival free from LVAD replacement or explant	Date of LVAD replacement or explant	• By device type • By the availability of transplant unit • By baseline characteristics of patients (age, sex, smoking, alcohol, BMI, FEVI, end-diastolic of LV comorbidities, previous cardiac interventions/devices and pharmacological therapies used)
Functional capacity	• 6-min walk test (6 MWT) • NYHA class	Not considered relevant by Delphi expert panel
Quality of life	• Kansas City Cardiomyopathy Questionnaire (KCCQ-12) • EuroQol-5D (EQ-5D)	Not considered relevant by Delphi expert panel
Patient or caregiver acceptability or satisfaction	Adaptation of the SATISCORE patient satisfaction questionnaire for cardiac surgery (Spanish)	Not considered relevant by Delphi expert panel
Health system impact/cost effectiveness		
Duration of a hospital stay for the implantation of the LVAD	• Date of admission • Date of discharge	Not considered relevant by Delphi expert panel
Length of stay in ICU post-intervention	• Date of ICU admission • Date of ICU discharge	Not considered relevant by Delphi expert panel
Length of stay during the hospital readmission in cardiology service	• Date of readmission in the cardiology service • Date of discharge from the readmission	Not considered relevant by Delphi expert panel
Length of stay in ICU readmission	• Date of readmission in ICU • Date of discharge from ICU readmission	Not considered relevant by Delphi expert panel

Abbreviations: CV=cardiovascular; FEV=forced expiratory volume; ICU=intensive care unit; LV=left ventricle; LVAD=left ventricular assist device; NYHA=New York Heart Association.

6. STATISTICAL ASPECTS

6.1 Sample size calculation

The calculation of the sample size was carried out considering one of the main outcomes of effectiveness of LVAD as destination therapy, the long-term survival rate (1.5–2 years of follow-up). The expected value of the outcome of interest taken from the ESPAMACS registry (90.9%) was compared with values observed in other registries such as EUROMACS (26.1%) [7] or INTERMACS (66%) [8] using a bilateral chi^2 test without

Hayes correction (Epidat version 4.2). A statistical power of 80% and a confidence level of 95% are assumed. In addition, the sample size obtained will be corrected by the percentage of loss of patients observed (M adjusted for losses = n (1/1-R), where n is the initial sample size and R is the percentage of losses). Taking into account previously mentioned INTERMACS registry data, it would be necessary to recruit 74 patients to achieve the statistical power and the assumed level of confidence. If the data from the EUROMACS registry (R=74%) are used, a sample size of 30 patients is obtained. It is considered that this assumption would be more feasible taking into account the experience published in the ESPAMACS registry.

One of the main objectives of this pilot is to assess possible levels of cross-border collaboration on RWD generation and exchange of the collected data. Therefore, the sample size of each registry has been previously established. As it is known, the number patients with ADHF who are candidates for LVAD as DT is very low. Then, the exchange of the collected data from different registries will increase the statistical power of the study. Moreover, it could give the opportunity to perform stratified analysis of safety and effectiveness evidence gaps identified previously.

6.2 Statistical analysis

The registry will include all consecutive patients treated with LVAD for DT.

The statistical analysis will consist of aggregated measures of the common predefined dataset set, i.e. mean or median of variables with a level of significance of 95% ($p<0.05$). Depending on sample size reached in the study, subgroup or stratified analysis based on stratification factors may be performed.

7. SETTING, DURATION AND FOLLOW-UP

Taking to account the aforementioned, the recruitment of patients would last over 6 years in order to reach the estimated sample size and the duration of the registry would be of at least 8 years in order to ensure that all patients complete the 2-year follow-up.

The baseline demographic and clinical variables would be collected before LVAD implantation. The variables related to the surgical procedure used or the safety of the implanted device would be recorded immediately after the intervention. The variables of safety (adverse events) and effectiveness will be collected at hospital discharge and at follow-up periods of 1 month, 3, 6, 9 and 12, 18 and 24 months. After 2 years, patients will be followed up once a year or until death or withdrawal from the study for other reasons (referral to heart transplant, loss of patient by address change, revocation of informed consent, etc.) until the maximum follow-up period of the registry so that all patients included on it are evaluated during at least 2 years.

In the event of a higher adverse events rate than expected or the appearance of serious adverse event not previously recorded, the implant centre is obliged to immediately notify the unit responsible for the LVAD registry (i.e. Scientific advice Unit, avalia-t). Then, this unit will communicate these incidents to the competent health authority in order to take the pertinent measures aimed at modifying the inclusion criteria of patients in the registry, the authorised devices or even the stoppage of the registry if necessary.

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Annex A. Variable definition for core outcome set

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
In- Hospital Death			
Death date	**Definition:** Date of death. **Supporting information:** Indicate the date of death for any cause. **Data type:** Date **Reporting source:** Medical records or administrative data.		DD/MM/ YYYY
Cause of death	**Definition:** The patient died since the previous visit/contact. This category includes all deaths regardless of cause of death. **Supporting information:** Primary cause. Cardiovascular vs non-cardiovascular 1= Cardiovascular death. Indicates cause of death was sudden cardiac death, MI, unstable angina, or other documented coronary artery disease; vascular death (e.g., stroke, arterial embolism, pulmonary embolism, ruptured aortic aneurysm, or dissection); congestive heart failure; or cardiac arrhythmia. Specify. 2= Non-cardiovascular death. Indicates cause of death was respiratory failure, pneumonia, cancer, trauma, suicide, or any other already defined cause (e.g., liver disease or renal failure). Specify. **Data type:** Categorical and nominal **Reporting source:** Medical records or clinician-reported	Cannon et al, 2001 ACC Clinical Data Standards	1= CV death 2= Non-CV death Specify
Cardiac adverse events			
Right-sided heart failure	**Definition:** Symptoms or findings of persistent right ventricular failure characterized by both of the following: a) Documentation of elevated central venous pressure (CVP) by a) Direct measurement with evidence of a CVP or right atrial pressure (RAP)>16 mmHg or b) Findings of significantly dilated inferior vena cava with absence of inspiratory variation by echocardiography or c) Clinical findings of elevated jugular venous distension at least half way up the neck in a upright patient. b) Manifestations of elevated central venous pressure characterized by: a) clinical findings of peripheral edema or b) Presence of ascites or palpable hepatomegaly on physical examination (unmistakable abdominal contour) or by diagnostic imaging or c) Laboratory evidence of worsening hepatic (total bilirubin>2.0 mg/dl) or renal dysfunction creatinine>2.0 mg/dl. **Supporting information:** If the patient meets the definition for right heart failure, the severity of the right heart failure will be graded according to the following scale below: 1= Mild RHF. Patient meets both criteria for RHF plus no readmissions for RHF since last surveillance period AND no inotropes since las surveillance period 2= Moderate RHF. Patients meets both criteria for RHF plus limited to one readmission for intravenous diuretics/vasodilators to treat RHF since las surveillance period AND no inotropes since las surveillance period 3= Severe RHF. Patient meets both criteria for RHF and need for inotropes at any time since last surveillance period OR two or more readmission for intravenous diuretics/vasodilators to treat RHF since last surveillance period, OR requiring RVAD support at any time after hospital discharge, OR death at any time following discharge from the VAD implant hospitalization with RHF as the primary cause. **Data type:** Categorical **Reporting source:** Medical records or clinician-reported.	INTERMACS Adverse Event Definition	1= Mild RHF 2= Moderate RHF 3= Severe RHF

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
Cardiac Arrhythmias	**Definition:** Any documented arrhythmia that results in clinical compromise (e.g., abnormal VAD function [e.g., diminished VAD flow or suction events], oliguria, pre-syncope or syncope, angina, dyspnea), or requires hospitalization or treatment (drug therapy, defibrillation, cardioversion, ICD therapy (e.g., shock or anti-tachycardia pacing) or arrhythmia ablation procedure) **Supporting information:** Cardiac arrhythmias are classified as 1 of 2 types: 1= Sustained ventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, defibrillation, cardioversion, ICD therapy, or arrhythmia ablation procedure. 2= Sustained supraventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, cardioversion, ICD therapy, or arrhythmia ablation procedure. **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	INTERMACS Adverse Event Definition	1= Sustained ventricular arrhythmia 2= Sustained supraventricular arrhythmia
Atrial fibrillation	**Definition:** Atrial fibrillation (AF) during the follow up period. **Supporting information:** Two categories of AF will be considered: 1= Paroxysmal. AF that terminates spontaneously or with intervention within 7 days of onset 2= Non-paroxysmal. Indicates AF permanent or cardioverter, after more than 7 days or onset. Permanent AF is when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	EACTS Adult Cardiac Database, Version 2.0 13 Dic 2018	1= Paroxysmal 2= Non-paroxysmal
	Definition: Atrial fibrillation (AF) during the follow up period. **Supporting information:** A new episode or acute recurrence of atrial arrhythmia documented by 1 of the following: -Atrial fibrillation/ flutter -Supraventricular tachycardia requiring treatment (supraventricular tachycardia that requires cardioversion , drug therapy, or is sustained for greater than 1 minute) 0= No 1= Yes **Reporting source:** Medical records or clinician-reported	Cannon et al, 2001 ACC Clinical Data Standards	0= No 1= Yes
Neurological adverse events			
Stroke	**Definition:** A stroke or cerebrovascular accident with loss of neurological function caused by an ischemic or haemorrhagic event with residual symptoms at least 24 hours after onset or leading to death. Includes haemorrhagic strokes, non-haemorrhagic stroke and unknown/no imaging performed. **Supporting information:** 0= Patient has not suffered a stroke 1= Patient has suffered a stroke **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	Cannon et al, 2001 ACC Clinical Data Standards	1= Haemorrhagic 2= Non haemorrhagic 3= Unknown/ no imaging performed

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
Stroke severity	**Definition:** Severity of stroke. **Supporting information:** Severity of stroke categorized as: 1= Left sided weakness 2= Right sided weakness 3= Left sided paralysis 4= Right sided paralysis 5= Speech deficit 6= Altered mental status 7= Coma 8= Other, specify **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	INTERMACS	1= Left sided weakness 2= Right sided weakness 3= Left sided paralysis 4= Right sided paralysis 5= Speech deficit 6= Altered mental status 7= Coma 8= Other, specify
	Definition: Stroke disability **Supporting information:** Disability measured at each visit and 90 days after the event using the modified Rankin Scale: 0= No symptoms at all 1= No significant disability despite symptoms; able to carry out all usual duties and activities 2= Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3= Moderate disability; requiring some help, but able to walk without assistance 4= Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5= Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6= Dead **Data type:** Categorical **Reporting source:** Patient-reported	CDISC. Standardized Definitions for CV and Stroke endpoint events in clinical trials. Karen A. Hicks, 2014	0= No symptoms 1= No significant disability 2= Slight disability 3= Moderate disability 4= Moderately severe disability 5= Severe disability 6= Dead
Type of stroke	**Definition:** A stroke or cerebrovascular accident with loss of neurological function caused by an ischemic or haemorrhagic event with residual symptoms at least 24 hours after onset or leading to death. **Supporting information:** Indicate the type of stroke following the next classification: Indicate the type of stroke: 1= Haemorrhagic: A stroke with documentation on imaging (e.g., CT scan or MRI of haemorrhage in the cerebral parenchyma, or a subdural or subarachnoid haemorrhage). Evidence of haemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis. 2= Non haemorrhagic: A focal neurological deficit that results from a thrombus or embolus (and not due to haemorrhage) that appears and is still partially evident for more than 24 hours 3= Unknown/no imaging performed: if the type of stroke could not be determined by imaging or other means (from lumbar puncture, neurosurgery, or autopsy) **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	Cannon et al, 2001 ACC Clinical Data Standards	1= Ischemic stroke 2= Haemorrhagic stroke 3= Unknown/ no imaging performed

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
Transient Ischemic Attack	**Definition:** Transient Ischemic Attack **Supporting information:** A focal neurological deficit (usually corresponding to the territory of a single cerebral vessel) that resolves spontaneously without any evidence of residual deficit at 24 hours 0= No 1= Yes **Data type:** Categorical **Reporting source:** Medical records or clinician reported	Cannon et al, 2001 ACC Clinical Data Standards	0= No 1= Yes
LVAD device-related adverse event			
Infection LVAD-related	**Definition:** Clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. **Supporting information:** The general categories of infection are listed below: 0= None. Patient had not a major infection LVAD related during the follow-up period. 1= Driveline infection. A positive culture from the skin and/or tissue surrounding the driveline coupled with the need to treat with antimicrobial therapy when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis. 2= Percutaneous Site and/or Pocket Infection. A positive culture from the skin and/or tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis. 3= Internal Pump Component, Inflow or Outflow Tract Infection. Infection of blood-contacting surfaces of the LVAD documented by positive site culture. (There should be a separate data field for paracorporeal pump that describes infection at the percutaneous cannula site, e.g. Thoratec PVAD) **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	INTERMACS	0= None 1= Driveline infection 2= Percutaneous Site and/or Pocket infection 3= Internal Pump component, inflow or Outflow Tract Infection

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
Pump thrombus	**Definition:** Pump Thrombus represents a special case of major device malfunction and can be delineated as suspected pump thrombus or confirmed pump thrombus. **Supporting information:** Pump thrombus will be classified as "suspected" based upon clinical, biochemical, or hemodynamic findings or "confirmed" based upon device inspection or incontrovertible radiologic studies or absence of appropriate Doppler flow signals that confirms thrombus within the device or its conduits that results in or could potentially induce circulatory failure. 0= None. LVAD had not a pump thrombus during the follow-up period. 1= Suspected pump thrombus is a pump-related malfunction in which clinical or MCSD parameters suggest thrombus on the blood contacting components of the pump, cannula, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria: a) Presence of hemolysis, b) Presence of heart failure not explained by structural heart disease, c) Abnormal pump parameters. One or more of the following events or interventions should accompany suspected pump thrombus: treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytic (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban); pump replacement; pump explant; stroke; arterial non-CNS thromboembolism; death. 2= Confirmed pump thrombus is a major pump-related malfunction in which thrombus is confirmed within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism. **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	INTERMACS	0= None 1= Suspected pump thrombus 2= Confirmed pump thrombus
LVAD failure	**Definition:** A device malfunction or failure **Supporting information:** Indicate if there was a device malfunction or failure during the follow-up period, classifying it by major or minor device failure. A failure is considered major when one of the following conditions occurs: suspected or confirmed pump thrombus (see below), pump replacement, pump explant, breach of integrity of driveline that required repair or death. A minor failure is when other conditions not described above occurs. 0= No. LVAD had not a major failure during the follow-up period 1= Minor. LVAD had a minor failure during the follow-up period 2= Major. LVAD had a major failure during the follow-up period **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	INTERMACS	0= No 1= Minor 2= Major
Aortic regurgitation	**Definition:** Aortic regurgitation **Supporting information:** Aortic regurgitation should be recorded on a qualitative scale. 0= None 1= Mild. RVol (ml/beat)<30; RF (%)<30; EROA (cm^2)<0.10 2= Moderate. RVol (ml/beat) 30-59; RF (%) 30-49; EROA (cm2) 0.10-0.29 3 = Severe: RVol (ml/beat) ≥60; RF (%)≥50 ; EROA (cm2) ≥30 **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	William A. Zoghbi, 2017. Valvular Regurgitation.	0= None 1= Mild 2= Moderate 3= Severe
Other serious adverse events			

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
ⓘSerious Adverse Event (SAE) is defined according to Meddev 2.7.3 guidelines on medical devices, adverse event that: a) led to a death, injury or permanent impairment to a body structure or a body function. b) led to a serious deterioration in health of the subject, that either resulted in: a life-threatening illness or injury, OR a permanent impairment of a body structure or a body function, OR in-patient hospitalization or prolongation of existing hospitalization, OR in medical or surgical intervention to prevent life threatening illness			
Renal dysfunction	**Definition:** Renal dysfunction includes patient suffering acute or chronic renal failure during the follow-up period. **Supporting information:** Two categories of renal dysfunction will be considered: 0= None. Patient has not suffered renal dysfunction during the follow up period. 1= Acute Renal Dysfunction. Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dl (in children, creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours. 2= Chronic Renal Dysfunction. An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days. **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	INTERMACS	0= None 1= Acute Renal Dysfunction. 2= Chronic Renal Dysfunction.
Respiratory failure	**Definition:** Includes patients suffering respiratory failure during the follow-up period. **Supporting information:** Impairment of respiratory function requiring reintubation, tracheostomy or the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures. 0= No. Patient had not respiratory failure during the follow-up period 1= Yes. Patient had respiratory failure during the follow-up period **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	INTERMACS	0= No 1= Yes
Hepatic dysfunction	**Definition:** An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ ALT) to a level greater than three times the upper limit of normal for the hospital. **Supporting information:** **Data type:** categorical **Reporting source:** Medical records or clinician-reported		0= No 1= Yes

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
Sepsis	**Definition:** Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) • Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection. -The baseline SOFA (Sequential [Sepsis-related] Organ Failure) score can be assumed to be zero in patients not known to have preexisting organ dysfunction. -A SOFA score ≥ 2 reflects an overall mortality risk of approximately10%in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted. In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs. Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA (quick SOFA). ie, alteration in mental status, systolic blood pressure ≦ 100 mmHg, or respiratory rate ≧ 22/min. • Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain main arterial pressure: MAP ≥ 65mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation. **Supporting information:** Indicate if patient had suffered a sepsis during the follow-up period categorized as following: 0= No. Patient have not suffered a sepsis during the follow-up period. 1= Sepsis. Patient have suffered a sepsis during the follow-up period. 2= Sepsis Shock. Patient have suffered a sepsis shock during the follow-up period. **Data type:** Categorical **Reporting source:** Medical record or clinician-reported	The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)	0= No 1= Sepsis 2= Sepsis Shock
	Definition: Sepsis is defined as having 2 or more of the SIRS (systemic inflammatory response syndrome) criteria AND a known or suspected infection. SIRS criteria included: -HR > 90 (acute and not a chronic condition) -Temp > 38.5 < 36.0ºC -Resp > 20 bpm or PaCO2 < 32 mmHg -White Blood Cells: WBC < 4000 or > 12000 or > 10% Bands Supporting information: Indicate if patient had suffered a sepsis during the follow-up period categorized as following: 0= No. Patient had not suffered a sepsis during the follow-up period. 1= Yes. Patient had suffered a sepsis during the follow-up period. **Data type**: Categorical **Reporting source**: Medical record or clinician-reported	EACTS Adult Cardiac Database, Version 2.0 13 Dic 2018	0= No 1= Yes

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
Organic multisystem failure	**Definition:** System for evaluating the appearance and evolution of Multiple Organ Failure in ICU patients. Assessments of the status of six organs or systems are used, and of some (vasoactive) treatment schemes (respiratory, cardiovascular, renal, hepatic (bilirubin level), coagulation, and CNS-Glasgow coma scale). **Supporting information:** Each of the organs is scored from 0 to 4. The score is the sum of all the isolated evaluations of the organs (total score = 0-16). A score other than zero and less than 3 is evaluated as organ dysfunction, while higher scores indicate multi-organ failure. 0 = score of 0-3 means organ dysfunction 1 = score> 3 means multi-organ failure **Data Type:** Categorical **Reporting source:** Medical records or clinician-reported	Sequential Organ Failure Assessment Score (SOFA)	0 = score of 0-3 means organ dysfunction 1 = score> 3 means multi-organ failure
Bleeding	**Definition:** Include life-threatening or disabling bleeding **Supporting information:** Bleeding is categorized as following: 1= Minor bleeding: any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life threatening, disabling or major. 2= Major bleeding: Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of two or three units of whole blood/RBC AND Does not meet criteria of life-threatening or disabling bleeding. 3=Life-threatening or disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR Overt source of bleeding with drop in haemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* (*Given one unit of packed RBC typically will raise blood haemoglobin concentration by 1g/dL, an estimated decrease in haemoglobin will be calculated) **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	Martin B. Leon, 2011. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials	1= Minor bleeding 2= Major bleeding 3= life-threatening or disabling bleeding
	Definition: Bleeding categorized by major bleeding or not. **Supporting information:** Major bleeding is defined as an episode of suspected internal or external bleeding that result in one or more of the following: a) death b) re-operation c) hospitalization d) transfusion of red blood cells. *Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event. 0= No. Patient has not suffered a major bleeding 1= Yes. Patient has suffered a major bleeding **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	INTERMACS	0= No 1= Yes

SAFETY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE / RESPONSE OPTION
	Definition: Bleeding categorized by severity as severe or life-threatening, moderate or mild. **Supporting information:** 1= Severe or life threatening. Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention 2= Moderate. Bleeding that requires blood transfusion but does not result in hemodynamic compromise 3= Mild. Bleeding that does not meet criteria for either **Data type:** Categorical **Reporting source:** Medical records or clinician-reported	GUSTO definition Sunil V. Rao 2006. A Comparison of the Clinical impact of bleeding	1= Severe 2= Moderate 3= Mild

EFFECTIVENESS			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Overall Survival			
Date of surgery	**Definition:** Date of surgery for LVAD implantation. **Supporting information:** Indicate the date on which the LVAD implantation surgery was performed. **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Date of death	**Definition:** Date of death from all causes **Supporting information:** Indicate the date of death of the patient for all causes **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Cause of death	**Definition:** The patient died since the previous visit/contact. This category includes all deaths regardless of cause of death. **Supporting information:** Primary cause. Cardiovascular vs non-cardiovascular 1= Cardiovascular death. Indicates cause of death was sudden cardiac death, MI, unstable angina, or other documented coronary artery disease; vascular death (e.g., stroke, arterial embolism, pulmonary embolism, ruptured aortic aneurysm, or dissection); congestive heart failure; or cardiac arrhythmia 2= Non-cardiovascular death. Indicates cause of death was respiratory failure, pneumonia, cancer, trauma, suicide, or any other already defined cause (e.g., liver disease or renal failure) **Data type:** Categorical and nominal **Reporting source:** Medical records or clinician-reported	Cannon et al, 2001 ACC Clinical Data Standards	1= CV death 2= Non CV death Specify
Event-free survival			
ⓘ To define event-free survival, indicate the degree of importance of including each of the events in the definition			
Date of surgery	**Definition:** Date of surgery for LVAD implantation. **Supporting information:** Indicate the date on which the LVAD implantation surgery was performed. **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Date of MI	**Definition:** Date on which the patient has suffered a myocardial infarction. **Supporting information:** Indicate the date on which the patient has suffered a myocardial infarction according to the definition given above. **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Date of Right Heart Failure	**Definition:** Date on which the patient has suffered a right heart failure (RHF) **Supporting information**: Indicate the date on which a moderate or severe RHF was detected according to the RHF definition given above **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Date of Cardiac Arrhythmia	**Definition:** The date on which the patient has suffered a cardiac arrhythmia. **Supporting information**: Indicate the date on which the patient has suffered a cardiac arrhythmia according to the definition given above. **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY

EFFECTIVENESS			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Date of Atrial fibrillation	**Definition:** The date on which an AF was detected. **Supporting information:** Indicate the date on which an AF was detected according to the RHF definition given above. **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Date of stroke	**Definition:** Date on which the patient has suffered a stroke. **Supporting information:** Indicate the date on which the patient has suffered a stroke according to the definition given above. **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Date of LVAD required repair / replacement/ explant	**Definition:** Date of LVAD replacement or explant **Supporting information:** Indicate the date on which the LVAD implantation surgery was performed. **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Date of other surgical interventions related to LVAD	**Definition:** Date of other surgical interventions related to LVAD **Supporting information:** Indicate the date on which other interventions were performed **Data type:** Date **Reporting source:** Medical records, clinician-reported or administrative data		DD/MM/ YYYY
Functional capacity			
6-minute walking distance (before and after LVAD)	**Definition:** 6 minute walk distance test **Supporting information:** This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD) **Data type:** Numerical **Reporting source:** Clinician-reported	https://www.atsjournals.org/doi/full/10.1164/ajrccm.166.1.at1102	Meters
NYHA class (before and after LVAD)	**Definition:** The New York Heart Association (NYHA) **Supporting information:** NYHA classification provides a simple way of classifying the extent of heart failure. It classifies patients in one of four categories based on their limitations during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain. The NYHA is free for all health care organizations, and a license is not needed. Please indicate the NYHA classification: 1= NYHA I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath). 2= NYHA II. Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath). 3= NYHA III. Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. 4= NYHA IV. Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. **Data type:** Categorical **Reporting source:** Clinician-reported	New York Heart Association	1= NYHA I 2= NYHA II 3= NYHA III 4= NYHA IV

EFFECTIVENESS			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
LVEF (pre and post-LVAD)	**Definition:** Left ventricular ejection fraction (LVEF) **Supporting information:** Please indicates the LVEF among the following categories: 1= Normal. LVEF 50% to 70% (midpoint 60%) 2= Mild dysfunction. LVEF 40% to 49% (midpoint 45%) 3= Moderate dysfunction. LVEF 30% to 39% (midpoint 35%) 4= Severe dysfunction. LVEF less than 30% **Data type:** Categorical **Reporting source:** Clinician-reported or medical records	American College of Cardiology	1= Normal 2= Mild dysfunction 3= Moderate dysfunction 4= Severe dysfunction
Quality of life			
KCCQ-12	**Definition:** Short version of the Kansas City Cardiomyopathy Questionnaire with 12 item (KCCQ-12) **Supporting information:** Is a self-administered 12-item questionnaire that quantifies physical limitations, symptoms, self-efficacy, social interference and quality of life. You can obtain a license to use this instrument at your institution by visiting https://www.cvoutcomes.org/licenses **Data type:** Numerical **Reporting source:** Patient reported	Kansas City Cardiomyopathy Qestionnaire-short version	
EQ-5D 5L version	**Definition:** The 5-level EQ-5D version (EQ-5D-5L) **Supporting information:** The user guide is available here: https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf **Data type:** Numerical **Reporting source:** Patient reported	https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/	
Patient or caregiver acceptability or satisfaction			
Satisfaction	**Definition:** It is a question about patient satisfaction Supporting information: Ask patient, “In general, how satisfied are you living with LVAD?”. Patient must respond according to the following 5-point Likert scale: 1=Very satisfied 2=Satisfied 3=Neither satisfied nor dissatisfied 4=Dissatisfied 5=Very dissatisfied **Data type:** Likert-scale **Reporting source:** Patient reported.	Adapted from SATISCORE Spanish questionnaire of satisfaction after cardiac surgery	5-point likert scale: 1=Very satisfied 2=Satisfied 3=Neither satisfied nor dissatisfied 4=Dissatisfied 5=Very dissatisfied
Acceptability	**Definition:** It is a question about patient acceptability **Supporting information:** Ask patient, "If you could go back in time, would you consider having surgery again?”. Patient must respond according to the following 5-point Likert scale: 1=Not at all 2=No 3=I don’t Know 4=Yes 5=Surely yes **Data type:** Likert-scale **Reporting source:** Patient reported.	Adapted from SATISCORE Spanish questionnaire of satisfaction after cardiac surgery	5-point likert scale: 1=Not at all 2=No 3=I don’t Know 4=Yes 5=Surely yes

HEALTH SYSTEM IMPACT/COST EFFECTIVENESS			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Economic and organizational impact			
Date of admission	**Definition:** Date of admission **Supporting information:** Indicate the date of admission pre-LVAD implantation **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY
Date of discharge	**Definition:** Date of discharge **Supporting information:** Indicate the date of discharge post-LVAD implantation **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY
Date of UCI admission	**Definition:** Date of UCI admission **Supporting information:** Indicate the date of UCI admission post-LVAD implantation **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY
Date of UCI discharge	**Definition:** Date of UCI discharge post-LVAD implantation **Supporting information:** Indicate the date of UCI discharge post-LVAD implantation **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY
Date of readmission in the cardiology service	**Definition:** Date of readmission (new admission post LVAD implantation) in the cardiology service **Supporting information:** Indicate the date **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY
Date of discharge from the cardiology readmission	**Definition:** Date of discharge from the readmission (new admission post LVAD implantation) in the cardiology service **Supporting information:** Indicate the date **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY
Date of readmission in other services due to adverse events related to LVAD	**Definition:** Date of readmission (new admission after LVAD implantation) in other services due to adverse events related to LVAD **Supporting information:** Indicate the date **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY
Date of discharge from the other hospital readmissions	**Definition:** Date of discharge from the hospital readmissions (new admission after LVAD implantation) in other services due to adverse events related to LVAD **Supporting information:** Indicate the date **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY
Date of readmission in UCI	**Definition:** Date of readmission (new admission after LVAD implantation) in UCI due to adverse events related to LVAD **Supporting information:** Indicate the date **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY

HEALTH SYSTEM IMPACT/COST EFFECTIVENESS			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Date of discharge from UCI readmission	**Definition:** Date of discharge from the readmission (new admission after LVAD implantation) in UCI due to adverse events related to LVAD **Supporting information:** Indicate the date **Data Type:** Date **Reporting source:** Administrative data		DD/MM/ YYYY

CHARACTERISTICS OF PATIENTS			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Age	**Definition:** Patient's age **Supporting information:** Please provide the patient's date of bird **Data Type:** Date **Reporting source:** Patient reported, medical records or administrative data		DD/MM/ YYYY
Sex	**Definition:** Patient's sex at bird **Supporting information:** Please provide the patient´s sex at bird **Data Type:** Categorical **Reporting source:** Patient reported, medical records or administrative data		1= Male 2= Female
BMI	**Definition:** Body mass index **Supporting information:** Weight and Height are used to calculate body mass index. Please indicate the weight and height of the patient. **Data type:** Numerical **Reporting source:** Clinician-reported or medical records		Weight in kilograms Height in centimeters
Smoking	**Definition:** It indicates if patient currently smoke or have smoked cigarettes or tobacco **Supporting information:** Choose from the following categories: 1= Current: Smoking cigarettes within 1 month of this admission 2= Recent: Stopped smoking cigarettes between 1 month and 1 year before this admission 3= Former: Stopped smoking cigarettes greater than 1 year before this admission 4= Never: Never smoked cigarettes **Data type:** Categorical **Reporting source:** Patient reported or clinician-reported from medical records	Cannon et al, 2001 ACC Clinical Data Standards	1= Current 2= Recent 3= Former 4= Never
Alcohol	**Definition:** This variable indicates if the patient regularly consumes alcohol **Supporting information:** This item is a patient reported measure. Please ask the patient, "do you drink more than one alcoholic drink a day?" (* Please, note that the definition of a standard unit of alcohol may differ between different countries, so it must be defined for each country). Item is phrased as a patient reported measure. However, if the patient is unable to answer, this information can be abstracted from the medical records. 0= No. Patient does not drink alcoholic drinks regularly or consume one or less standard alcoholic drinks per day 1= Yes. Patient drink more than one standard alcoholic drink per day **Data type:** Categorical **Reporting information:** Patient reported or clinician-reported from medical records	ICHOM *modified	0=No 1=Yes

COMORBIDITIES			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Diabetes	**Definition:** It indicates if patient is diabetic **Supporting information:** Please indicate if patient has diabetes mellitus 0=No. Patient has not diabetes mellitus 1= DM type 1. Patient has type 1 diabetes mellitus 2= DM type 2. Patient has type 2 diabetes mellitus **Data type:** Categorical **Reporting source:** Clinician-reported or medical records		0= Not diabetic 1= DM type 1 2= DM type 2

	Definition: History of diabetes, regardless of duration of disease. **Supporting information:** Need for antidiabetic agents or a fasting blood sugar greater than 7 mmol/l or 126 mg/dl. If yes, the type of diabetic control should be noted: 1= Not treatment 2= Diet treatment 3= Oral agent treatment 4= Insulin treatment (includes any combination of insulin) 5= Subcutaneous (not insulin) **Data type:** Categorical **Reporting source:** Clinician-reported or medical records	Cannon et al, 2001 ACC Clinical Data Standards	1= Not treatment 2= Diet 3= Oral 4= Insulin 5= Subcutaneous
Renal dysfunction	**Definition:** This variable indicates if patient has a diagnosis of renal dysfunction **Supporting information**: Indicate if the patient has or has had renal dysfunction in the past 0= No renal dysfunction 1= Renal dysfunction without dialysis 2= Renal dysfunction that requires dialysis **Data type:** Categorical **Reporting source:** Clinician-reported or medical records		0=None 1=Renal dysfunction no dialysis required 2=Renal dysfunction dialysis required
Hepatic dysfunction	**Definition:** Indicates if patient has a hepatic dysfunction **Supporting information:** Hepatic dysfunction is defined as an increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital 0= No. Patient has not a hepatic dysfunction 1= Yes. Patient has a hepatic dysfunction **Data type:** Categorical **Reporting source:** Clinician-reported or medical records		0= No 1= Yes
Chronic lung disease	**Definition:** This variable indicates if patient has chronic lung disease as COPD, emphysema or asthma **Supporting information:** This item include COPD, asthma and emphysema when patient requires medication (inhalers, aminophylline or steroids) for chronic pulmonary disease, has an FEV1 less than 75% predicted value; venous pO2<60 mmHg, pCO2>50 mmHg, or has intermittent or allergic reversible airways disease treated with bronchodilators or steroids 0= No. Patient has not chronic lung disease 1= Mild. FEV1 60% to 75% of predicted, and/or on chronic inhaled or oral bronchodilator therapy 2= Moderate. FEV1 50% to 59% of predicted, and/or on chronic oral/systemic steroid therapy aimed at lung disease. 3= Severe. FEV1< 50% and/or Room Air pO2< 60 or pCO2>50 **Data type:** Categorical **Reporting source:** Clinician-reported or medical records	EACTS Adult Cardiac Database, Version 2.0 13 Dec 2018	0= No 1=Mild 2=Moderate 3=Severe
Dyslipidemia	**Definition:** Indicate if the patient has a history of dyslipidemia that was diagnosed and/or treated by a physician **Supporting information:** Hypercholesterolemia is defined as elevation on serum cholesterol requiring dietary or drug treatment 0= No. Patient has not hypercholesterolemia requiring treatment (diet or drug) 1= Yes. Patient has hypercholesterolemia requiring dietary or drug treatment **Data type:** Categorical **Reporting source:** Clinician-reported or medical records	EACTS Adult Cardiac Database, Version 2.0 13 Dec 2018	0= No 1= Yes

Hypertension	**Definition:** Past medical history of hypertension. **Supporting information:** Indicate if the patient has a history of hypertension that was diagnosed and/or treated by a physician. 0= No hypertension 1= Hypertension **Data type:** Categorical **Reporting source:** Clinician-reported or medical records	EACTS Adult Cardiac Database, Version 2.0 13 Dec 2018	0= No 1= Yes

CARDIOVASCULAR HISTORY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Prior LVEF	**Definition:** Left ventricular ejection fraction (LVEF) **Supporting information:** Please indicates the LVED among the following categories: 1= Normal. LVEF 50% to 70% (midpoint 60%) 2= Mild dysfunction. LVEF 40% to 49% (midpoint 45%) 3= Moderate dysfunction. LVEF 30% to 39% (midpoint 35%) 4= Severe dysfunction. LVEF less than 30% **Data type:** Categorical **Reporting source:** Clinician-reported or medical records	America College of Cardiology	1= Normal 2= Mild dysfunction 3= Moderate dysfunction 4= Severe dysfunction
Prior arrhythmia	**Definition:** History of arrhythmia **Supporting information:** Any documented arrhythmia that results in clinical compromise (e.g., abnormal VAD function [e.g., diminished VAD flow or suction events], oliguria, pre-syncope or syncope, angina, dyspnea), or requires hospitalization or treatment (drug therapy, defibrillation, cardioversion, ICD therapy (e.g., shock or anti-tachycardia pacing) or arrhythmia ablation procedure). Cardiac arrhythmias are classified as 1 of 2 types: 0= Patient has not history of arrhythmia 1= Sustained ventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, defibrillation, cardioversion, ICD therapy, or arrhythmia ablation procedure 2= Sustained supraventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, cardioversion, ICD therapy, or arrhythmia ablation procedure **Data type:** Categorical **Reporting source:** Clinician-reported or medical records		0= No arrhytmia 1= Sustained ventricular arrhytmia 2= Sustained supraventricular arrhytmia
Prior AF	**Definition:** History of Atrial Fibrillation (AF) **Supporting information:** Please indicates if patient has a history of AF. Two categories of AF will be considered: 0= No. Patient has not history of AF. 1= Paroxysmal. AF that terminates spontaneously or with intervention within 7 days of onset 2= Non-paroxysmal. Indicates AF permanent or cardioverter, after more than 7 days or onset. Permanent AF is when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm **Data type:** Categorical **Reporting source:** Clinician-reported or medical records	EACTS Adult Cardiac Database, Version 2.0 13 Dec 2018	0= No 1= Paroxysmal 2= Non-paroxysmal
Prior MI	**Definition:** Previous myocardial infarction (MI) **Supporting information:** Please indicate if patient have had a heart attack or myocardial infarction. According to 2018 Fourth Universal Definition of Myocardial Infarction, any one of the following criteria meets the diagnosis for prior MI: a) Abnormal Q waves with or without symptoms in the absence of non-ischemic causes b) Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology c)Patho-anatomical findings of a prior MI.Pathological Q waves with or without symptoms in the absence of non-ischemic causes 0= No. Patient had not previous MI 1= Yes. Patient had a previous MI **Data type:** Categorical **Reporting source:** Clinician-reported, patient-reported or medical records	Mervyn Singer, 2015. Fourth Universal Definition of MI	0= No 1= Yes

CARDIOVASCULAR HISTORY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Prior Stroke	**Definition:** Indicate whether the patient has a history of cerebrovascular event **Supporting information:** Please indicate if patient has a history of Stroke nor Transient Ischemic Attack defined as following: 0= None 1= Ischemic Stroke. Defined as an acute episode of focal cerebral, spinal or retinal dysfunction caused by infarction of central nervous system tissue 2= Haemorrhagic Stroke. Defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular or subarachnoid haemorrhage 3= TIA. Defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction **Data type:** Categorical **Reporting source:** Clinician-reported or medical records		1= None 1= Ischemic Stroke 2= Hemorrhagic Stroke 3= TIA
Prior PVD	**Definition:** Prior peripheral vascular disease (PVD) **Supporting information:** Indicate if patient has peripheral vascular disease (PVD) defined as claudication, >50% stenosis/previous or planned intervention on the abdominal aorta, limb arteries, amputation for arterial disease. PVD excludes disease of thoracic aorta. 0= No. Patient has history of PVD 1= Yes. Patient has not history of PVD **Data type:** categorical		0= No 1= Yes
Prior cardiac surgery	**Definition:** Previous cardiac surgery requiring opening the pericardium **Supporting information**: Indicate if patient had a previous cardiac surgery requiring opening of the pericardium 0= No. Patient had not a previous cardiac surgery 1= Yes. Patient had a previous cardiac surgery requiring opening of the pericardium **Data type**: Categorical **Reporting source:** Medical records	EACTS Adult Cardiac Database, Version 2.0 13 Dec 2018	0= No 1= Yes
Prior LVAD	**Definition:** Patient has an prior LVAD implanted **Supporting information:** Patient has an implanted LVAD that must be replaced. Identify the device trademark from implant card providing the following information: the identification of the device, including the device name, serial number, lot number, the UDI, the device model, as well as the name, address and the website of the manufacturer **Data type:** Categorical **Reporting source:** Medical records	REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices.	Device trademark

CARDIOVASCULAR HISTORY			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Pacemaker, CRT or ICD	**Definition:** This variable offers information on whether the patient has had a previous pacemaker, Cardiac Resynchronization Therapy (CRT) or Implantable Cardioverter Defibrillator (ICD) **Supporting information:** Indicate if patient has a pacemaker, CRT or ICD 0= No. Patient has not a pacemaker, ICR or RCT 1= Pacemaker. Patient has a permanent pacemaker 2= ICD. Patient has an implantable cardioverter-defibrillator 3= CRT. Patient has a Cardiac Resynchronization Therapy Pacemaker/Defibrillator **Data type:** Categorical **Reporting source:** Medical records		0= No 1= Pacemaker 2= ICD 3= CRT
PCI or CABG	**Definition**: This variable offers information on whether the patient has had a previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). **Supporting information:** Indicate if the patient underwent PCI, placement of an angioplasty guidewire, balloon, or other device (e.g., stent, atherectomy, brachytherapy, or thrombectomy catheter) into a native coronary artery or CABG for the purpose of mechanical coronary revascularization 0= No. Patient had not a previous PCI or CABG 1= PCI. Patient had a previous PCI 2= CABG. Patient has a previous CABG **Data type:** Categorical **Reporting source:** Medical records and/or patient report		0= No 1= Yes

PHARMACOLOGICAL MANAGEMENT			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Cardiovascular drugs	**Definition:** Pharmacological treatment for cardiac therapy. **Supporting information:** For all the medications listed below their use before hospital admission and at hospital discharge should be noted: (Classification according to the ATC WHO 2019 Guidelines) 1= C01 Cardiac Therapy 2= C02 Antihypertensives 3= C03 Diuretics 4= C04 Peripheral vasodilators 5= C07 Beta blocking agents 6= C08 Calcium Channel Blockers 7= C09 Agents Acting on the renin-angiotensin system 8= C10 Lipid modifying agents **Data Type:** Categorical **Reporting source:** Medical records	ATC WHO 2019 Guidelines	1= C01 Cardiac Therapy 2= C02 Antihypertensives 3= C03 Diuretics 4= C04 Peripheral vasodilators 5= C07 Beta blocking agents 6= C08 Calcium Channel Blockers 7= C09 Agents Acting on the renin-angiotensin system 8= C10 Lipid modifying agents
Antithrombotic agents	**Definition:** Treatment with antithrombotic agents. **Supporting information:** For all the medications listed below their use before hospital admission and at hospital discharge should be noted: (Classification according to the ATC WHO 2019 Guidelines) 1= B01AA Vitamin K antagonists. This group comprises vitamin K antagonists such as dicoumarol, warfarin, etc. 2= B01AB Heparin group 3= B01AC Platelet aggregation inhibitors excl. heparin 4=B01AE Direct thrombin inhibitors 5=B01AF Direct factor Xa inhibitors 6= B01AX Other antithrombotic agents **Data type:** Categorical **Reporting source:** Medical records	ATC WHO 2019 Guidelines	1= B01AA Vitamin K antagonists. 2= B01AB Heparin group 3= B01AC Platelet aggregation inhibitors excl. heparin 4=B01AE Direct thrombin inhibitors 5=B01AF Direct factor Xa inhibitors 6= B01AX Other antithrombotic agents

Other outcomes			
VARIABLE/ MEASURE	VARIABLE DEFINITION	REFERENCE	MEASURE RESPONSE OPTION
Device type			
Device trademark	**Definition:** Device trademark **Supporting information:** Identify the device trademark from implant card providing the following information: the identification of the device, including the device name, serial number, lot number, the UDI, the device model, as well as the name, address and the website of the manufacturer **Data Type:** nominal **Reporting source:** Administrative data or implant card	REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices	
Hospital centre requirements			
Availability of transplant unit	**Definition:** Availability of transplant unit in the hospital **Supporting information:** Indicate if there is a transplant unit with a implement transplant program in the hospital **Data Type:** Categorical 0= No 1= Yes **Reporting source:** Administrative data		0= No 1= Yes