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

Common Evidence Gaps report

April 2021

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Pilot team

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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 the 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

Agenas	*Agenzia Nationale per I servizi sanitari regionali*
BTT	*Bridge to transplantation*
DT	*Destination therapy*
EQ-5D	*EuroQol-5 Dimensions*
EU	*European Union*
EUnetHTA	*European Network of Health Technology Assessment*
GDMT	*Guideline-directed medical therapy*
HF	*Heart failure*
HTA	*Health technology assessment*
KCCQ	*Kansas City Cardiomyopathy Questionnaire*
KCE	*Belgian Health Care Knowledge Centre*
LVAD	*Left ventricular assist device*
MLHFQ	*Minnesota Living with Heart Failure Questionnaire*
NICE	*National Institute for Health and Care Excellence*
NYHA	*New York Heart Association*
OMM	*Optimal medical management*
PICO	*Population, intervention, comparator and outcome*
PLEG	*Post-launch evidence generation*
RWD	*Real-world data*
SF-36	*Short Form-36*
UK	*United Kingdom*
WP	*Work package*

1 BACKGROUND

1.1 Aim and rationale of the pilot

This pilot was conducted within the European Network of Health Technology Assessment (EUnetHTA) Joint Action 3 Work Package (WP) 5, the aim of which is to help in generating optimal and robust evidence for health technologies (pharmaceuticals or others) throughout the technology lifecycle, bringing benefits for patient access and public health.

Work Package 5 consists of two strands: strand A focuses on initial evidence generation and the activity of Early Dialogues, while strand B focuses on post-launch evidence generation (PLEG). More information on the specific WP5B activities can be found at https://eunethta.eu/pleg/.

This document is an output of a WP5B PLEG product-specific pilot on the left ventricular assist device (LVAD) for destination therapy (DT). The main WP5B pilot steps are presented in Figure 1.

This pilot was proposed by the Scientific Advice Unit (avalia-t) considering the uncertainties noted during the national health technology assessment (HTA). The proposal was supported by the following considerations:

- LVADs are used as circulatory support to help the damaged left ventricle 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 DT).
- 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. Current evidence supports that these modern devices can improve health outcomes in patients who are not candidates for transplant but shows that LVADs can have serious post-implant complications, including stroke and microvascular bleeding.
- 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 these 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.

The main objectives of this pilot are therefore as follows:

- To build a common and agreed data set for collection (which will serve as a basis for common analysis afterwards);
- To gather locally generated data (when possible) from different sources (databases, registries, health care records); and
- To assess possible levels of cross-border collaboration on the generation and exchange of real-world data (RWD).

The present report corresponds to step four of the pilot, and its aim is to synthesise the main evidence gaps and research needs identified by pilot team members in their national HTA (performed at different time points after centralised marketing authorisation approval/CE mark).

This work will form the basis for the next step of the pilot (step 5) which will consist of agreeing on the common data set for RWD collection for this product. This common data set will reflect the basis of RWD collection individually set up on a national level by pilot team members.

The final report (step 6) will possibly include RWD from different sources; however, its main goal is to present lessons and issues of any kind related to international collaborations on RWD. This will be key information to pave the way towards effective future collaborations on PLEG.

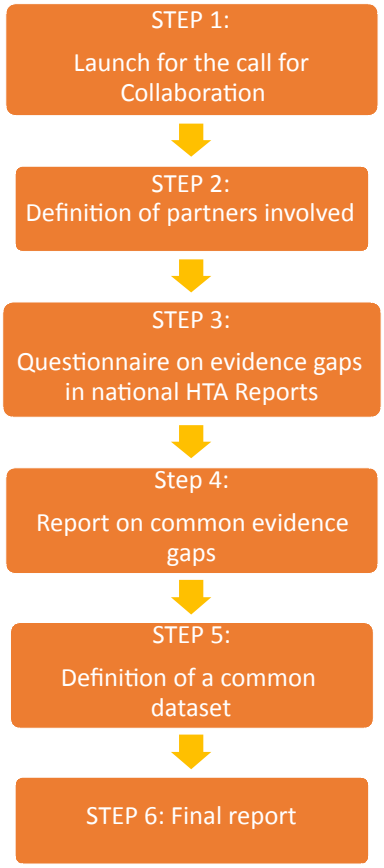

Figure 1. Main steps of the pilot

1.2 Overview of the disease or health condition

Advanced HF

HF is a worldwide epidemic that increases significantly the expenditure of the health care systems [1]. The prevalence of HF in Europe is estimated to be around 2–3% of the general population, of which 0.4% have advanced HF [2].

When the HF is advanced, pharmacological and dietary treatment is no longer effective. In these cases, heart transplantation is considered the treatment of choice, although it is limited by the organ availability and waiting time until a compatible organ is available [3].

In this context, circulatory mechanical assist devices, especially LVADs, are an option as a bridge to heart transplantation. Besides, LVADs may be used as DT in patients who have a permanent contraindication to heart transplantation, as this is the main therapeutic option [4,5].

1.3 LVAD for DT: main characteristics

LVADs are mechanical pumps that generate a circulatory flow, which allows partially or totally replacing the function of the heart. They generate a circulatory flow that depends specifically on the device considered. 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 an external console with a microprocessor that allows control of the pump function and collects information from it. The necessary system energy is supplied either by two batteries, or by a battery and electric current. System data storage and adjustment of external console parameters are carried out using a touch screen computer equipped with specific software. There are various types of devices that 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 bridge to transplantation (BTT), recovery, and rarely as DT [5].

1.3.1 Regulatory status of LVAD for DT

Currently there are four LVADs approved by the European Union (EU) to be used as DT: HeartMate 3™, HeartWare HVAD™ System™, Incor® and Jarvik 2000. Some of these also have authorisation for the indication of DT in other countries (Table 1).

Table 1. Regulatory status and approved indications of LVAD

Name device	CE mark Year/indication	FDA Year/indication	Other authorisation Year/indication
Jarvik 2000	2005: bridge to transplantation and destination therapy	2000: bridge to transplantation 2012: destination therapy (Investigational Device Exemption-IDE G100124)[a]	Japan 2013 (indication not provided)
HeartMate 3™ Left ventricular assist device (LVAD)	2015: bridge to transplantation/recovery or destination therapy	2017: bridge to transplantation/recovery (Investigational Device Exemption – MOMENTUM 3-Multicentre Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3™)[b]	Not provided
HeartWare™ HVAD™ System	2009: bridge to transplantation 2012: destination therapy	2012: bridge to transplantation or recovery 2017: destination therapy	Not provided
Incor®	Bridge to transplantation/recovery Destination therapy	Not provided	Not provided
HeartMate II®	2005 (indication not provided)	2008: bridge to transplantation 2010: destination therapy	Canada 2014: bridge to transplantation and destination therapy
HeartMate® VE/ XVE (HeartMate I)	Not provided	2003: destination therapy	Not provided

From: [a] http://www.hfsa.org/wp-content/uploads/2014/06/jarvik+relive+poster.pdf and https://www.jarvikheart.com/about-us/company-timeline/; [b] Heatley G, Sood P, Goldstein D, Uriel N, Cleveland J, Middlebrook D, Mehra MR; MOMENTUM 3 Investigators. Clinical trial design and rationale of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3™ (MOMENTUM 3) investigational device exemption clinical study protocol. J Heart Lung Transplant. 2016;35(4):528-36.

Updated January 2021.

1.3.2 HTA status of LVAD for DT

In Spain, 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) [6]. It was requested by the Commission on Benefits, Insurance and Financing of the Spanish National Health System, to assess available evidence regarding the clinical effectiveness and safety of LVADs as DT, as well as to analyse the costs and the organisational, ethical, social and legal aspects that may condition their implementation in the Spanish National Health System.

The National Institute for Health and Care Excellence (NICE) published an interventional procedure (IP) (overview) based on a rapid review and specialist opinion about the safety and efficacy of LVAD for DT in people ineligible for heart transplantation in 2014 (https://www.nice.org.uk/guidance/ipg516/documents/ipg516-implantation-of-a-left-ventricular-assist-device-for-destination-therapy-in-people-ineligible-for-heart-transplantation-overview2) [7].

In 2015, Agenas developed a HTA report aimed to assess the safety and clinical efficacy of using a LVAD in addition to guideline-directed medical therapy (GDMT) (including cardiac resynchronisation therapy defibrillator, implantable cardioverter-defibrillator and cardiac resynchronisation therapy defibrillator) in adult patients with end-stage HF who are not eligible or immediately eligible for cardiac transplant. Moreover, evidence on organisational aspects and cost-effectiveness of LVAD was also included in the report (http://www.salute.gov.it/imgs/C_17_ReportDispositivi_13_documentoInglese_inglese_itemName_0_documentoENG.pdf) [8].

The aim of the HTA report conducted by the Belgian Health Care Knowledge Centre (KCE) was to evaluate the safety, clinical effectiveness and cost-effectiveness of LVAD as DT or as a bridge of candidacy (https://kce.fgov.be/sites/default/files/atoms/files/KCE_264_LVAD_report.pdf) [9].

Table 2 presents the HTA status of LVAD for destination therapy among pilot team members.

Table 2. HTA status among pilot team members

HTA body	HTA status	Date of assessment finalisation
Avalia-t (ES)	Finalised	May 2018 (HTA report published; only summary in English)
NICE (UK)	Finalised	December 2014 (HTA report published)
KCE (BE)	Finalised	April 2016 (HTA report published)
Agenas (IT)	Finalised	October 2015 (HTA report published)

Updated January 2021.

Abbreviations: BE=Belgium; ES=Spain; HTA= Health Technology Assessment; IT=Italy; KCE= Belgian Health Care Knowledge Centre; NICE= National Institute for Health and Care Excellence; UK=United Kingdom.

1.3.3 Reimbursement status of LVAD for DT

The reimbursement of LVADs is a matter of debate in many EU countries, being in most only indicated for temporary support while patients await transplant or recovery.

Table 3 shows the reimbursement status of LVAD for DT by country for the pilot team.

Table 3. Reimbursement status across countries

Country	Reimbursement status	Decision date
Spain	Ministry of Health (MoH) order SSI/1356/2015 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 destination therapy (permanent or long-term) for patients who are not candidates for heart transplantation.	02/07/2015
UK	No reimbursement decision is available for the stated indication.	Not available
Belgium	The National Institute for Health and Disability Insurance (NIHDI) provides reimbursement for a yearly number of 50 LVADs for patients listed for transplantation (BTT) or in whom transplantation may be anticipated (BTC). There is presently no reimbursement for LVADs as destination therapy (DT).	Not available
Italy	Not provided	Not available

Updated January 2021.

Abbreviations: BTC=bridge to candidacy; BTT=bridge to transplantation; HF=heart failure; LVAD=left ventricular assist device; UK=United Kingdom.

2 MAIN ASSESSMENT RESULTS AND COMMON EVIDENCE GAPS FROM NATIONAL HTAS

The main uncertainties identified in the 2018 report done by the Scientific Advice Unit (avalia-t) [6] were related to the safety and to the eligibility criteria for the appropriate selection of the best candidates for LVADs as DT. This means determining which patients would obtain the best outcomes with regard to their comorbidities or previous interventions/clinical history. Important gaps have also been identified in relation to the durability of the LVADs and the long-term management of these patients, i.e. device replacement and hospital readmissions management. This information is essential to estimate the organisational and total cost impact of these devices, as costs could be related to implantation, replacement or removal of the device.

The uncertainties detected were shared with the NICE, the KCE and the Agenzia Nationale per I servizi sanitari regionali (Agenas) which had previously performed their respective LVAD assessments (NICE, 2014 [7]; Agenas, 2015 [8]; KCE, 2016 [9]). A questionnaire (Appendix 1) to collect evidence gaps and research needs identified by the pilot team members in their national HTA was elaborated based on the EUnetHTA position paper on how to best formulate research recommendations for primary research arising from the HTA. The questionnaire was completed by the pilot team members. The questionnaire comprised two main sections:

1. Assessment results and

2. Recommendations for research

Based on the responses received, the pilot team identified and highlighted commonalities, which are presented in Sections 2.1–2.3.

2.1 Main body of evidence assessed in the national HTAs

The main studies on LVAD for DT assessed in national HTAs of pilot team members are described below.

The following studies provided results pertaining to the safety and effectiveness domain:

(1) One HTA report carried out by Health Quality Ontario published in 2016 [10] included one HTA report and two systematic reviews:

- The objective of a HTA report elaborated by NICE (2015) [7] was to determine the effectiveness of both continuous flow-second generation (e.g. HeartMate II®) and pulsatile flow-first generation (e.g. HeartMate® XVE) LVADs as destination therapy. One registry (INTERMACS), three randomised clinical trials, the REMATCH trial, a non-randomised comparative study and four case studies were included in that HTA report (n=2795 patients).

- A systematic review performed by Boothroyd et al. (2012) [11] that assessed the clinical effectiveness of two DAVI continuous flow devices (HeartMate II® and HeartWare™ HVAD™ System) as a BTT and DT. Three studies were included, two of them already included in the previous NICE report.

- A systematic review was carried out by US Department of Veterans Affairs in 2012 [12], the aim of which was to assess the clinical effectiveness of pulsatile (HeartMate® XVE) and continuous (HeartMate II®) LVADs. This included:

(2) Comparative studies:

- A multicentre randomised clinical trial (ENDURANCE) [13], conducted in 48 US centres, compared patients treated with axial continuous flow LVAD (HeartMate II®) (n=297) and centrifugal continuous flow (HeartWare™ HVAD™ System) (n=148) in a 1:2 ratio.

- The objective of a non-randomised comparative study (ROADMAP study) of 200 patients who were candidates for ventricular support under the indication of DT, but who were not dependent on inotropic treatment, from 41 centres in the USA, was to determine the safety and effectiveness of the LVAD continuous flow (HeartMate II®) (n=97) vs. optimal medical management (OMM) (n=103) [14].

(3) Observational studies:

- Two retrospective analyses of the INTERMACS registry [15,16]. One study assessed the frequency of “poor outcome” (a compound variable defined as death or mean score on the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) scale <45) after implantation of a continuous or pulsatile flow LVAD in 1638 patients with advanced HF who were not candidates for transplantation. In the other study, survival and quality of life at 1 year were analysed in 1470 patients with advanced HF who were not candidates for transplantation after implantation of a continuous flow LVAD stratified by age (<60 years, 60–69 years and >70 years).

- Two case series that included <20 patients with advanced HF who were not candidates for transplantation and who received a HeartMate II® continuous flow axial LVAD in one case [17] or a HeartWare™ HVAD™ System centrifuge in another [18].

Three qualitative studies that assessed patients and/or caregiver experiences with an LVAD as DT through personal interviews and used a thematic analysis of the results. The sample size ranged from 7 to 20 patients/caregivers and they were all conducted in the USA [19–21].

Ten studies assessed the ethical impact of the implementation of an LVAD as DT. Four of these were qualitative studies in which semi-structured interviews were carried out with patients, caregivers and health workers to gather the opinions of all the individuals involved in the decision-making process of LVAD as DT [22–25]. The remaining six were narrative reviews dealing with ethical aspects to be taken into account in the process [26–31].

The economic impact of implementing LVAD as DT was evaluated in the systematic review carried out by Health Quality Ontario [10] and two cost-effectiveness studies; one evaluated continuous-flow LVADs and the other analysed the HeartMate® device [32], although both also compared these with OMM [33].

2.2 Assessment results and common evidence gaps

The main assessment results and evidence gaps identified at national level are reported in Tables 4–6.

Different outcomes, i.e. safety, effectiveness, satisfaction of patients/caregivers and cost-effectiveness/budget impact related to use of LVAD as DT are considered to be subject to uncertainties on national team members’ HTA reports.

2.2.1 Safety

Only two observational studies include perioperative or 30-day mortality (Estep et al., 2015 [14]; Haeck et al., 2015 [18]). Likewise, there is insufficient evidence regarding serious adverse events (such as neurological events, right HF, respiratory failure, renal failure or bleeding) produced in the medium to long term.

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. There are no eligibility criteria for the appropriate selection of the best candidates for LVADs as DT (patients who would obtain the best outcomes in relation to their comorbidities or previous interventions/clinical history).

2.2.2 Effectiveness

Most studies included 2-year survival and the longest follow-up period reported was 4 years (Rogers et al., 2017 [13]), so the survival in the longer term is unknown, as well as the durability of the device or the need for a replacement beyond 2 years.

Event-free survival is defined differently in different studies, therefore a common definition of event-free survival is required.

Effectiveness is measured through the determination of the New York Heart Association (NYHA) class before and after the intervention. The exercise capacity is tested through the 6-min walk test. In both cases, it is measured before the intervention and at 3 months or 1 year. Only one study (Rogers et al., 2017 [13]) provides NYHA class at 2 years. The long-term functional status and the progression or recurrence of the target disease is therefore another of the uncertainties raised by the evaluation agencies.

The degree of rehospitalisation is another aspect relatively unknown and yet is deemed highly important due to its influence on the quality of life and because of the economic impact that entails.

Different instruments are used to assess health related quality of life in patients with HF include disease-specific measures, such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ), the KCCQ, and generic measures such as the EuroQol-5 Dimensions (EQ-5D) or SF-36 test. The quality of life is generally measured at 1-year post-implant, but it is unknown in the longer term.

2.2.3 Satisfaction and acceptability of the patient and/or caregiver

Uncertainty exists regarding the acceptability of the devices. Several studies that assessed this outcome indicated that, in some cases, patients and above all, caregivers suffered an important emotional distress due to the important burden associated with caring for patients requiring LVAD as a DT, while in other studies, patients highlighted the opportunity the device has offered in terms of improvement in their quality of life.

Studies focused on the ethical aspects related to LVAD therapy highlighted the need for specifically designed informed consent forms for patients with advanced HF that are offered LVAD as a definitive therapy. Moreover, clinicians should ensure that patients understand the high complication rates associated with this procedure.

2.2.4 Cost-effectiveness, budget impact and organisational impact

According to evidence published, LVAD as DT showed an important incremental cost-effectiveness ratio compared with OMM. However, the cost data concerning LVAD as DT could be limited. As we highlighted before, 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 in long-term therapy.

In addition to the uncertainties regarding the cost impact of LVAD as DT, 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 have not been well analysed yet.

Likewise, the patient selection and patient management are crucial for a cost-effectiveness evaluation and they should be carefully assessed when implementing a LVAD implantation programme and its governance.

Table 4. Assessment results for the safety domain

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7	Outcome 8
	In-hospital death (% patients)	**Neurological events (% patients)**	**Pump thrombosis (% patients)**	**Sepsis (% patients)**	**Right-sided heart failure (% patients)**	**Bleeding (% patients)**	**Driveline infection (% patients)**	**Other relevant adverse events (% patients)**
Health Quality Ontario (2016) [10] HTA report	**No data**	Related with device flow CF vs. PF Haemorrhagic stroke: **CF: 8 PF: 7** Ischaemic stroke: **CF: 11 PF: 8** at 2 years Related with baseline characteristics/treatment of patients: no data	**4–5 at 2 years** Related with device flow CF vs PF: **CF: 4–5 PF: 0** at 2 years Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data	Related with device flow CF vs. PF: **CF: 36 PF: 44** at 2 years Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data	Related with device flow CF vs. PF: **CF: 24 PF: 32** at 2 years Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data	**76 at 2 years** Related with trademark device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/treatment of patients: no data	**28 at 2 years** Related with trademark device: no data Related with device flow CF vs PF: no data Related with baseline characteristics/treatment of patients: no data	Related with device flow CF vs. PF: Respiratory dysfunction: **CF: 38 PF: 41** Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data
Certainty/ quality of evidence[a]	No data	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Rogers et al. (2017) [13] ENDURANCE RCT	**No data**	Stroke **12.1–29.7** at **2 years** Haemorrhagic stroke: **4 at 2 years** Related with trademark device: Stroke: **HW: 29.7** **HM: 12.1** Haemorrhagic stroke: **HW: 14.9** **HM: 4.0** Ischaemic stroke: **HW: 17.6** **HM: 8,1** at 2 years Related with baseline characteristics/treatment of patients: no data	**No data**	Related with device flow CF vs. PF: no data Related with trademark device: **HW: 23.6 HM: 15.4** at 2 years Related with baseline characteristics/treatment of patients: no data	Related with trademark device **HW: 38.5** **HM: 26.8** at 2 years Related with device flow CF vs. PF: no data Related with baseline characteristics/treatment of patients: no data	Related with trademark device **HW: 60.1** **HM: 60.4** at 2 years Related with device flow CF vs. PF: no data Related with baseline characteristics/treatment of patients: no data	Related with trademark device **HW: 19.6** **HM: 15.4** at 2 years Related with device flow CF vs. PF: No data Related with baseline characteristics/ treatment of patients No data	Renal dysfunction: **12.1 at 2 years** Related with device flow CF vs. PF: no data Related with trademark device Hepatic dysfunction: **HW: 4.7** **HM: 8.1** Renal dysfunction: **HW: 14.9** **HM: 12.1** Respiratory dysfunction: **HW: 29.1** **HM: 25.5** Arrhythmia: **HW: 37.8** **HM: 40.9** Related with baseline characteristics/treatment of patients: no data

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7	Outcome 8
	In-hospital death (% patients)	**Neurological events (% patients)**	**Pump thrombosis (% patients)**	**Sepsis (% patients)**	**Right-sided heart failure (% patients)**	**Bleeding (% patients)**	**Driveline infection (% patients)**	**Other relevant adverse events (% patients)**
Certainty/ quality of evidence[a]	No data	Moderate	No data	Moderate	Moderate	Moderate	Moderate	Moderate
Estep et al. (2015) [14] Non-randomised clinical trial ROADMAP study	**No data**	Stroke: **8.5 at 1 year** Haemorrhagic stroke: **4.3 at 1 year** Ischaemic stroke: **5.3 at 1 year** Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data	**6.4 at 1 year**	**No data**	**No data**	**47 at 1 year** Related with trademark device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/treatment of patients: no data	**9.6 at 1 year** Related with trademark device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/treatment of patients: no data	Arrhythmia **18.1–40.9 at 1 year** Related with device flow CF vs. PF: no data Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data
Certainty/ quality of evidence[a]	No data	Very low	Very low	No data	No data	Very low	Very low	No data
Arnold et al. (2016) [15] INTERMACS Registry	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**
Certainty/ quality of evidence[a]	No data	No data	No data	No data	No data	No data	No data	No data

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7	Outcome 8
	In-hospital death (% patients)	**Neurological events (% patients)**	**Pump thrombosis (% patients)**	**Sepsis (% patients)**	**Right-sided heart failure (% patients)**	**Bleeding (% patients)**	**Driveline infection (% patients)**	**Other relevant adverse events (% patients)**
Samson et al. (2016) [17] Observational study	**No data**	Stroke: **40 at 3 years** Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data	**39 at an average of 376 days** Related with device flow CF vs. PF: no data Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data	**No data**	**46.7 at 3 years** Related with device flow CF vs. PF: no data Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data	**86.7 at 3 year** Related with trademark device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/treatment of patients: no data	**26.7 at 3 years** Related with trademark device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/treatment of patients: no data	**No data**
Certainty/ quality of evidence[a]	No data	Very low	Very low	No data	Very low	Very low	Very low	No data
Grady et al. (2015) [16] INTERMACS Registry	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**
Certainty/ quality of evidence[a]	No data	No data	No data	No data	No data	No data	No data	No data
Haeck et al. (2015) [18] Observational study	**25% (n=2 patients)** Related with personnel training, device flow CF vs PF, trademark device, baseline characteristics/treatment of patients: no data	**No data**	**No data**	**5.8 (n=1 patient) at 2 years**	**13 < 30 days** Related with device flow CF vs. PF: no data Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data	**No data**	**No data**	Renal dysfunction: **38 at 2 years** Related with device flow CF vs. PF: no data Related with trademark device: no data Related with baseline characteristics/treatment of patients: no data

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7	Outcome 8
	In-hospital death (% patients)	**Neurological events (% patients)**	**Pump thrombosis (% patients)**	**Sepsis (% patients)**	**Right-sided heart failure (% patients)**	**Bleeding (% patients)**	**Driveline infection (% patients)**	**Other relevant adverse events (% patients)**
Certainty/ quality of evidence[a]	Very low	No data	No data	Very low	Very low	No data	No data	Very low

[a]Evaluated by GRADE.
Abbreviations: CF=continuous flow pump; CS=qualitative Study; HM=HeartMate II®; HW=HeartWare ™ HVAD ™; GR=GRADE scale; OS=observational study; PF=pulsing flow pump; RCT=randomised clinical trial; SR=systematic review.

Table 5. Assessment results for the effectiveness domain

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7
	Overall survival (% patients)	**Event-free survival rate (% patients)[a]**	**Functional capacity[b]**	**Durability of the LVADs or device failure % (patients)**	**Long-term management (% patients)**	**Quality of life**	**Satisfaction and acceptability of the patient and/or caregiver**
Health Quality Ontario (2016) [10] HTA report	**16 at 4 years** Related with device flow CF vs. PF **CF: 76 PF: 68 at 1 year** **CF: 67 PF: 45 at 2 years** Related with the device: no data Related with baseline characteristics/ treatment of patients: no data	**54 at 2 years** Related with device flow CF vs. PF **CF: 96 PF: 83 at 1 year** Related with the device: no data Related with baseline characteristics/ treatment of patients: no data	Related with device flow CF vs PFCF: 318 PF: 306 at 1 year Related with the device: no data Related with baseline characteristics/ treatment of patients: no data	**Pump replacement: 34 at 2 years** Related with device flow CF vs. PFCF: 9 PF: 34 at 2 years Related with the device: no data Related with baseline characteristics/ treatment of patients: no data	**No data**	**EQ-5D (score) 3 months: 70 (HM)** **2 year: 70 (HM)** Related with device flow CF vs. PF **KCCQ (score)** CF: 65.9 PF: 59.1 at 1 years **MLHFQ (score)** CF: 34.1 PF: 44.4 at 1 year Related with the device: no data Related with baseline characteristics/ treatment of patients: no data	**No data**
Certainty/ quality of evidence[c]	Moderate	Moderate	Moderate	Moderate	No data	Moderate	No data
Rogers et al. (2017) [13] Endurance RCT	Related with the device **HW: 60.2 HM: 67.6** **at 2 years** Related with device flow CF vs PF: no data Related with baseline characteristics/ treatment of patients: no data	Related with the device **HW: 55.0 HM: 57.4** **at 2 years** Related with device flow CF vs PF: no data Related with baseline characteristics/ treatment of patients: no data	Related with the device at 3 months: HW: 199.4±183.4 HM: 190.1±159.01 Related with device flow CF vs PFCF: no data Related with baseline characteristics/ treatment of patients: no data	Related with the device **Device malfunction or failure: 25.5-31.4** at 2 years Related with device flow CF vs. PFCF: no data Related with baseline characteristics/ treatment of patients: no data	Related with the device **Rehospitalisation** **HW: 84.1** **HM: 79.2** Related with device flow CF vs. PFCF: no data Related with baseline characteristics/ treatment of patients: no data	Related with the device **EQ-5D (score increased) at 3 months** HW: 22.5 HM: 25.5 **KCCQ (score increased)** HW: 25.8 HM: 25.3 Related with device flow CF vs. PFCF: no data Related with baseline characteristics/ treatment of patients: no data	**No data**
Certainty/ quality of evidence[c]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	No data

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7
	Overall survival (% patients)	**Event-free survival rate (% patients)[a]**	**Functional capacity[b]**	**Durability of the LVADs or device failure % (patients)**	**Long-term management (% patients)**	**Quality of life**	**Satisfaction and acceptability of the patient and/or caregiver**
Estep et al. (2015) [14] Non-randomised clinical trial ROADMAP study	**82±4 at 1 year** Related with the device: no data Related with device flow CF vs PF: no data Related with baseline characteristics/ treatment of patients: no data	**80±4 at 1 year** Related with the device: no data Related with device flow CF vs PF: no data Related with baseline characteristics/ treatment of patients: no data	**75 (187–263) at 1 year** Related with the device: no data Related with device flow CF vs PF: no data Related with baseline characteristics/ treatment of patients: no data	**No data**	**79.8 at 1 year** Related with the device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/ treatment of patients: no data	**EQ-5D (score increased) 29 (41 to 70) at 1 year** Related with the device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/ treatment of patients: no data	**No data**
Certainty/ quality of evidence[c]	Moderate	Moderate	Moderate	No data	Moderate	Very low	No data
Arnold et al. (2016) [15] INTERMACS Registry	**77.6 at 1 year** Related with the device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/ treatment of patients: no data	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**
Certainty/ quality of evidence[c]	Very low	No data	No data	No data	No data	No data	No data
Samson et al. (2016) [17] Observational study	**72.2 at 1 year** **37 at 2 years** **37 at 3 years** Related with the device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/ treatment of patients: no data	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**
Certainty/ quality of evidence[c]	Very low	No data	No data	No data	No data	No data	No data

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7
	Overall survival (% patients)	**Event-free survival rate (% patients)[a]**	**Functional capacity[b]**	**Durability of the LVADs or device failure % (patients)**	**Long-term management (% patients)**	**Quality of life**	**Satisfaction and acceptability of the patient and/or caregiver**
Grady et al. (2015) [16] INTERMACS Registry	Related with the device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/ treatment of patients <60 years, 77 60–69 years, 74 >70 years, 73 at 1 year	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**
Certainty/ quality of evidence[c]	Very low	No data	No data	No data	No data	No data	No data
Haeck et al. (2015) [18] Observational study	**75 at 6 months** Related with the device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/ treatment of patients: no data	**No data**	**300 at 6 months** Related with the device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/ treatment of patients: no data	**No data**	**No data**	**MLHFQ** 3 months: 40 6 months: 25 Related with the device: no data Related with device flow CF vs. PF: no data Related with baseline characteristics/ treatment of patients: no data	**No data**
Certainty/ quality of evidence[c]	Very low	No data	Very low	No data	No data	Very low	No data

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7
	Overall survival (% patients)	**Event-free survival rate (% patients)[a]**	**Functional capacity[b]**	**Durability of the LVADs or device failure % (patients)**	**Long-term management (% patients)**	**Quality of life**	**Satisfaction and acceptability of the patient and/or caregiver**
Marcuccilli et al. (2014) [21] **Kitko et al. (2013) [20]** **Brush et al. (2010) [19]**	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**	Concerns regarding: • the need to modify the lifestyle • the fear and anxiety caused by the new situation as well as the stress related to the decision-making process both to implement it and to withdraw it • difficulties that supposes the device in the daily life of the patients

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7
	Overall survival (% patients)	**Event-free survival rate (% patients)[a]**	**Functional capacity[b]**	**Durability of the LVADs or device failure % (patients)**	**Long-term management (% patients)**	**Quality of life**	**Satisfaction and acceptability of the patient and/or caregiver**
Certainty/ quality of evidence[c]	No data	No data	No data	No data	No data	No data	GRADE-CERQual: moderate

[a]Event-free survival=survival free from disabling stroke or LVAD urgent replacement.
[b]To be evaluated by 6-min walk distance post LVAD (metres). NYHA class pre-LVAD vs. post-DAV was not evaluated.
[c]To be evaluated by GRADE.
Abbreviations: CF=continuous flow; EQ-5D=EuroQol-5 dimensions; HM=HeartMate II®; HW=HeartWare ™; KCCQ=Kansas City Cardiomyopathy Questionnaire; MLHFQ=Minnesota Living with Heart Failure Questionnaire; PF=pulsatile flow; SF-36=Short Form-36.

Table 6. Assessment results for the cost-effectiveness, budget impact and organisational impact domain

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5
	Cost-utility analysis	**Cost-effectiveness analysis**	**Cost impact due to rehospitalisation, replacement or removal of the device**	**Organisational impact**	**Patient and caregivers teaching**
Chew et al. (2017) [32] Cost-effectiveness analysis Markov-model-based study	**ICER: $230,692/QALY or $193,975/LY** compared with OMM (Canadian dollars)	**No data**	**Cost of implantation per case** (including cost of device and hospitalisation) **$182,600 ($91,300–$273,900)** (2015 Canadian dollars) **Yearly rehospitalisation for LVAD $25,859**[b] (2015 Canadian dollars)	**No data**	**No data**
Certainty/quality of evidence[a]	Moderate	No data	Moderate	No data	No data
Health Quality Ontario (2016) [10] Systematic review	**ICER:** a) **€107,600/QALY (95% CI, €66,700–€181,100)** compared with OMM b) **€94,100/life-year gained (95% CI, €59,100–€160,100**) compared with OMM	**ICER: $198,184/QALY $167,208/life-year gained** compared with OMM (United States dollars)	**No data**	**No data**	**No data**
Certainty/quality of evidence[a]	Moderate	Moderate	Moderate	No data	No data
Clegg et al. (2007) [33] Cost-effectiveness analysis Markov-model-based study	**No data**	**ICER**: **170,616£/QALY** compared with OMM	**No data**	**No data**	**No data**
Certainty/quality of evidence[a]	No data	Moderate	No data	No data	No data

[a]Evaluated by GRADE.
[b]Estimated by cost of rehospitalisation ($9795 [$6850–$30,627]) and annual rate of rehospitalisation for CF-LVAD (per patient year) (2.64 [1.32–3.96]).
Abbreviations: ICER=incremental cost-effectiveness ratio; LY=life years; OMM=optimal medical management; QALY=quality-adjusted life years.

2.3 Common research recommendations

These research recommendations are reported according to the PICO (population, intervention, comparator and outcome) scheme, as recommended in the guidance included in the position paper on how to best formulate research recommendations for primary research arising from HTA reports.

The research recommendations arising from the evidence gaps identified and indicated by each pilot team member are reported in detail in Tables 7 and 8. Recommendations were developed from common evidence gaps identified by pilot HTA bodies.

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.

Table 7. Summary of the uncertainties identified by each of the HTA bodies

Uncertainties/gaps identified	Avalia-t	NICE	KCE	Agenas
Safety				
• In-hospital death (30-day mortality)	X		X	
• Adverse events	X	X	X	X
• Influence of the LVAD devices on safety	X	X	X	X
• Patient eligibility for LVAD	X	X	X	X
• Need for specialised cardiology units	X	X		X
Effectiveness				
• Overall survival	X	X	X	X
• Event-free survival	X	X	X	X
• Exercise capacity	X	X	X	
• Functional status	X	X	X	
• Heart recovery		X		
• Device-related morbidity	X	X	X	X
• Durability of the device	X	X	X	X
• Hospital re-admission	X	X	X	
• Progression and recurrence of the target disease	X		X	X
• Influence of the LVAD devices on effectiveness	X			X
• Quality of life	X	X	X	
Satisfaction and acceptability of the patient and/or caregiver				
• Satisfaction and acceptability of the patient and/or caregiver	X			
• Information for patients	X	X		
Cost-effectiveness, budget impact and organisational impact				
• Cost impact	X	X	X	X
• Cost-effectiveness	X		X	X
• Organisational impact (needs of medical/nursing)	X	X	X	X
• Patients and caregivers training	X			X

Abbreviations: KCE= Belgian Health Care Knowledge Centre; LVAD=left ventricular assist device; NICE= National Institute for Health and Care Excellence.

Table 8. Compiled research recommendations according to the PICO

	Population	Intervention	Comparator	Outcome	Other questions
1	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	Patients who are candidate to LVAD as destination therapy but reject it; therefore they would receive OMM	Adverse events	Not required
2	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	LVAD	Influence of the LVAD devices on safety Comparison of the two devices (i.e. HeartWare™ vs. HeartMate®)	Not required
3	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	Patients who are candidate to LVAD as destination therapy but reject it; therefore they would receive OMM	Patient eligibility for LVAD Patients of each group should be stratified by main baseline characteristics or co-morbidities (i.e. diabetes mellitus, right ventricular function, main organ function, prior MI, prior stroke, prior cardiac interventions, etc.)	Not required
4	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	Patients who are candidate to LVAD as destination therapy but reject it; therefore they would receive OMM	Overall survival	Not required
5	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	Patients who are candidate to LVAD as destination therapy but reject it; therefore they would receive OMM	Event free survival (survival free from disabling stroke or LVAD urgent replacement)	Not required

	Population	Intervention	Comparator	Outcome	Other questions
6	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	LVAD	Device-related morbidity Comparison of two LVAD devices (i.e. HeartWare ™ vs. HeartMate®)	Not required
7	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	Patients who are candidate to LVAD as DT but reject it; therefore they would receive OMM	Durability of the device	Not required
8	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	Patients who are candidate to LVAD as DT but reject it; therefore they would receive OMM	Cost impact	Not required
9	Patients with end-stage HF who are candidates for LVAD implantation and who also are not eligible for heart transplantation such as age and/or co-morbidities	LVAD	Patients who are candidate to LVAD as DT but reject it; therefore they would receive OMM	Organisational impact (medical/nursing needs)	Not required

Abbreviations: MI= myocardial infarction; DT=destination therapy; HF=heart failure; LVAD=left ventricular assist device; OMM=optimal medical management.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. Circulation. 2015;4(131):e29-e322.
2. Trochu JN, Leprince P, Bielefeld-Gomez M, Bastien O, Beauvais F, Gueffet JP, et al. Left ventricle assist device: when and which patients should we refer? Arch Cardiovasc Dis. 2012;105(2):114-21.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37:2129-200.
4. Sanchez-Enrique C, Jorde UP, Gonzalez-Costello J. Heart transplant and mechanical circulatory support in patients with advanced heart failure. Rev Esp Cardiol (Engl Ed). 2017;70(5):371-81.
5. Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transplant. 2010;29(4 Suppl):S1-39.
6. Puñal Riobóo J, Varela Lema L. Dispositivo de asistencia ventricular izquierda (DAVI) como terapia de destino. Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del SNS. Agencia Gallega para la Gestión del Conocimiento en Salud (ACIS), Unidad de Asesoramiento Científico-técnico, Avalia-t; 2018. Report.
7. National Institute for Health and Care Excellence (NICE). Interventional procedure overview of implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation. National Institute for Health and Care Excellence (NICE); 2014. Report.
8. Gillespie F, Abraha I, Amicosante AMV, Caimmi PP, Chiarolla E, Corio M, et al. LVAD (Left Ventricular Assist Device) in addition to guideline directed medical therapy (GDMT) in end stage heart failure. Rome, Italy: Agenzia Nazionale per il Sevizi Sanitari Regionali, AGENAS; 2015. Report.
9. Neyt M, Leroy R, Devos C, Van Brabandt H. Left ventricular assist devices in the treatment of end-stage heart failure. Belgian Health Care Knowledge Centre (KCE); 2016. Report.
10. Health Quality Ontario. Left ventricular assist device for destination therapy: a health technology assessment; 2016 http://www.hqontario.ca/Portals/0/Documents/evidence/reports/hta-lvad-1602-en.pdf (accessed 02 Jan 2018).
11. Boothroyd LJ, Lambert LJ, Sas G, Guertin JR, Ducharme A, Charbonneau E, et al. Should eligibility for heart transplantation be a requirement for left ventricular assist device use? Recommendations based on a systematic review. Can J Cardiol. 2013;29(12):1712–20.
12. Rector TS, Taylor BC, Greer N, Rutks I, Wilt TJ. Use of left ventricular assist devices as destination therapy in end-stage congestive heart failure: a systematic review. US Department of Veteran's Affairs; 2012 https://www.ncbi.nlm.nih.gov/books/NBK99059/pdf/Bookshelf_NBK99059.pdf (accessed 02 Jan 2018).
13. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. New Engl J Med. 2017;376(5):451–60.
14. Estep JD, Starling RC, Horstmanshof DA, Milano CA, Selzman CH, Shah KB, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: results from the ROADMAP study. J Am Coll Cardiol. 2015;66(16):1747–61.
15. Arnold SV, Jones PG, Allen LA, Cohen DJ, Fendler TJ, Holtz JE, et al. Frequency of poor outcome (death or poor quality of life) after left ventricular assist device for destination therapy: results from the INTERMACS registry. Circ Heart Fail. 2016;9(8) doi: 10.1161/CIRCHEARTFAILURE.115.002800.
16. Grady KL, Naftel DC, Myers S, Dew MA, Weidner G, Spertus JA, et al. Change in health-related quality of life from before to after destination therapy mechanical circulatory support is similar for older and younger patients: analyses from INTERMACS. J Heart Lung Transplant. 2015;34(2):213–21.
17. Samson R, Rajapreyar I, Jaiswal A, Payne B, Cassidy M, Weaver M, et al. Device thrombosis during destination therapy. Am J Med Sci 2016;351(5):441–6.
18. Haeck ML, Beeres SL, Hoke U, Palmen M, Couperus LE, Delgado V, et al. Left ventricular assist device for end-stage heart failure: results of the first LVAD destination program in the Netherlands. Neth Heart J. 2015;23(2):102–8.
19. Brush S, Budge D, Alharethi R, McCormick AJ, MacPherson JE, Reid BB, et al. End-of-life decision making and implementation in recipients of a destination left ventricular assist device. J Heart Lung Transplant. 2010;29(12):1337–41.
20. Kitko LA, Hupcey JE, Gilchrist JH, Boehmer JP. Caring for a spouse with end-stage heart failure through implantation of a left ventricular assist device as destination therapy. Heart Lung. 2013;42(3):195–201.
21. Marcuccilli L, Casida JM. From insiders' perspectives: adjusting to caregiving for patients with left ventricular assist devices. Prog Transplant. 2011;21(2):137–43.
22. Magid M, McLlvennan CK, Jones J, Nowels CT, Allen LA, Thompson JS, et al. Exploring cognitive bias in destination therapy left ventricular assist device decision making: a retrospective qualitative framework analysis. Am Heart J. 2016;180:64–73.
23. McIlvennan CK, Jones J, Allen LA, Lindenfeld J, Swetz KM, Nowels C, et al. Decision-making for destination therapy left ventricular assist devices: implications for caregivers. Circ Cardiovasc Qual Outcomes. 2015;8(2):172–8.

24. McIlvennan CK, Matlock DD, Narayan MP, Nowels C, Thompson JS, Cannon A, et al. Perspectives from mechanical circulatory support coordinators on the pre-implantation decision process for destination therapy left ventricular assist devices. Heart Lung. 2015;44(3):219–24.
25. Thompson JS, Matlock DD, McIlvennan CK, Jenkins AR, Allen LA. Development of a decision aid for patients with advanced heart failure considering a destination therapy left ventricular assist device. JACC Heart Fail. 2015;3(12):965–76.
26. Chamsi-Pasha H, Chamsi-Pasha MA, Albar MA. Ethical challenges of deactivation of cardiac devices in advanced heart failure. Curr Heart Fail Rep. 2014;11(2):119–25.
27. Dudzinski DM. Ethics guidelines for destination therapy. Ann Thorac Surg. 2006;81(4):1185–8.
28. Gafford EF, Luckhardt AJ, Swetz KM. Fast facts and concepts #269. Deactivation of a left ventricular assist device at the end-of-life. Mayo Clinic; 2015. Available at: www.mypcnow.org (accessed 21 May 2018).
29. Mueller PS, Swetz KM, Freeman MR, Carter KA, Crowley ME, Severson CJ, et al. Ethical analysis of withdrawing ventricular assist device support. Mayo Clin Proc. 2010;85(9):791–7.
30. Panke JT, Ruiz G, Elliott T, Pattenden DJ, DeRenzo EG, Rollins EE, et al. Discontinuation of a left ventricular assist device in the home hospice setting. J Pain Symptom Manage. 2016;52(2):313–7.
31. Rizzieri AG, Verheijde JL, Rady MY, McGregor JL. Ethical challenges with the left ventricular assist device as a destination therapy. Philos Ethics Humanit Med. 2008;3:20.
32. Chew DS, Manns B, Miller RJH, Sharma N, Exner DV. Economic evaluation of left ventricular assist devices for patients with end stage heart failure who are ineligible for cardiac transplantation. Can J Cardiol. 2017;33(10):1283–91.
33. Clegg AJ, Scott DA, Loveman E, Colquitt J, Royle P, Bryant J. Clinical and cost-effectiveness of left ventricular assist devices as destination therapy for people with end-stage heart failure: a systematic review and economic evaluation. Int J Technol Assess Health Care. 2007;23(2):261–8.

APPENDIX 1. QUESTIONNAIRE ON EVIDENCE GAPS_TEMPLATE

Agency	
Country	
Contacts	
HTA assessment status	Finalised Ongoing Further comments: free text
Evidence gaps identified in the HT assessment	Please indicate the domain in which evidence gaps have been identified during HTA (Multiple answers are possible if needed): Clinical effectiveness Safety Cost effectiveness Budget impact Condition of use Personnel recruitment and training Others (please specify)
Research question	Please provide the details on the evidence gaps and the research question(s) according to the following template:

Evidence gaps

Assessment results

For each outcome, specify the main assessment results in terms of the quality and quantity of available evidence (number of studies, type of studies), and, if applicable, the estimate of the effect size and the level of confidence in the estimate. ***Please clarify the evidence gaps for each outcome of your assessment, sorted by the level of importance:***

Outcome- level of importance 1	Outcome- level of importance 2	Outcome- level of importance 3	Outcome- level of importance 4	Outcome- level of importance 5

Recommendations for research

Question with clear rationale: potential relationship between intervention and important outcomes.

Please report the research question, for each evidence gap reported here above, according to the PICO.

Additional questions should be presented in the column "Other questions".

Population	Intervention	Comparator	Outcomes	Time Stamp	Other questions

Population or sub population of interest. *Example: to collect data patients with a mild, adult onset course (previously categorized as type IV SMA)*	The technology/ intervention and setting of use *Example: To collect data on the most appropriate dose to be used for the different patients*	Relevant comparator and setting of use	Outcomes of interest (1-5) *Example: To collect long term efficacy data*	Date when the recommendation was issued, alternatively the date of the HTA assessment finalization or the date when this form has been filled out	E.g. number of patients, duration of treatment

Table adapted from the "Position Paper on how to best formulate research recommendations for primary research arising from HTA" https://www.eunethta.eu/wp-content/uploads/2016/01/EUnetHTA-Position-Paper-on-research-recommendations.pdf