CPAG Summary Report for Clinical Panel – Mechanical assist devices for circulatory support (destination therapy) in people with advanced heart failure - URN 1693

The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	There is a survival benefit [A]	Survival depends on the severity of heart failure. This is measured by the INTERMACS scoring system (profile). The most reliable estimate of survival for people with advanced heart failure who received a ventricular assist device (VAD) was from the analysis by Jorde et al 2014. They found that 74% and 61% of patients were alive at 12 and 24 months respectively. This is consistent with the most recent estimated probability of survival analysis from the INTERMACS registry report (Kirklin et al 2015) of recipients implanted between 2012 and 2014. This reports survival at 12 months and three years of 76% and 57% respectively. With ordinary medical management (OMM) only 20% of comparable patients are likely to be alive at one year, though no studies directly compare VAD with ordinary medical management. The evidence suggest that VAD implantation offers a significant improvement in survival.
2.	Progression free survival	Not measured	
3.	Mobility	Benefit determined [A]	Physical Function (6MWD): This is a measure of physical function using the six-minute walk distance test. This is usually performed on a treadmill, and the distance in metres that the patient

			can walk during 6 minutes is measured. In the study by Jorde et al 2014, 19% of VAD recipients were able to complete a walk test test. Before implant, the mean distance walked was 183m. Two years post implant, this had increased to 297m. It is not clear how much extra distance is a meaningful in a real-life setting. An extra 114m may be a highly important difference if the person is initially unable to walk. If the initial distance is 183m, then it is unclear how this translates to being able to perform activities of daily living. This result should be treated with caution as it includes only a small subset (19%) of the recruited study population (n=247) who were initially ambulatory. Although the study was a prospective post approval study, there is no comparative data for 6MWD for patients treated with ordinary medical management.
4.	Self-care	Benefit determined [B]	EQ-5D problems with self-care: Pre-implantation, 287 out of 668 (43%) people had difficulties with self-care. This was reduced to 32%, 26 % and 25% at 3 months, 6 month and 12 months post device implant. This indicates that VAD implant is associated with meaningful reduction in problems with self-care, and that this is sustained throughout 3 months to 12 months post implant period. This was based on a single, large, observational, uncontrolled registry study with significant selection bias. Also, the registry excludes patients who died before discharge. In addition, there were significantly fewer patients included in the analysis at 12

			months compared to baseline. This may understate the complications associated with receiving a VAD.
5.	Usual activities	Benefit determined [B]	EQ-5D problems with usual activities.Pre-implantation, 543 out of 667 (81%) people had difficulties with usual activities. This was reduced to 54%, 46% and 44% at 3 months, 6 months and 12 months post device implant. This indicates a meaningful reduction in problems with performing usual activities, and that this is sustained throughout the 3 months to 12 months post implant period. This was based on a single, large, observational, uncontrolled registry study with significant selection bias. The registry excludes patients who died before discharge. In addition, there were significantly fewer patients included in the analysis at 12 months compared to baseline. This may understate the complications associated with receiving a VAD.
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	These were reported within a number of different composite quality of life measures reported in detail below
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [A]	Adverse events were significant with the most common being bleeding. A large proportion of VAD recipients will experience a bleed during the first 24 months after device implant. Jorde et al (2014) reported that over 54% of recipients had a bleed which required

			transfusion and 13% needed further surgery. Other common adverse events included infection (sepsis, local device related infection, non-device related infection), stroke (haemorrhagic stroke, ischaemic stroke) and device related events such pump thrombosis and device malfunction. These are reported in detail below.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1	30 day mortality	B	30-day mortality is the likelihood of dying within 30 days of the VAD implantation operation. Six out of the 176 (3.4%) VAD recipients died within 30 days. All of the six deaths occurred in people with baseline INTERMACS profiles 1 or 2. For people with very severe advanced heart failure (INTERMACS profiles 1 and 2 in particular), the chances of surviving and recovering from the implantation procedure needs to be carefully considered as this, combined with the lower likelihood of survival at 12 months indicates that the benefit of VAD implantation may be limited for these recipients. This was based on weak evidence from a single, small, uncontrolled study of 176 subjects all treated at a 'non-transplant' centre. The results may not be generalisable to the UK and should be treated with caution.

2	% patients discharged after implantation	B	The proportion of VAD recipients who were successfully discharged from hospital post implantation surgery was 90%. This means that 10% of patients did not survive the implantation procedure or peri-operative period. Although specific reasons for lack of discharge were not described, careful consideration about patient selection needs to be made in order to achieve the best survival outcomes reported in the clinical trials. This was based on weak evidence from a single, small, uncontrolled study of 176 subjects all treated at a 'non-transplant' centre in the USA. The results may not be generalisable to the UK and should be treated with caution.
3	% free from device event	B	This is the proportion of VAD recipients who were free from having a 'device event' at a specified point in time. A device event could include malfunction of the device, pump replacement, device related infection. During the 2 year period after implant, there were an estimated 33 device events across the 1160 CF device recipients. The proportions who were free of a device event were 99%, 96% and 94% at 6 months, 12 months and 24 months respectively. This indicates that the proportion of VAD recipients who will have a device related event is initially low but there is a small increase in these events as the duration of living with the device increases.

			This was based on actuarial survival which should be treated with caution as it estimates the probability of survival and adverse events beyond the time period for which there are observed events. The data are from a single, large, uncontrolled registry study.
4	Attainment of NYHA 1 or II	A	This is a measure of symptom improvement from NYHA functional class IV to NYHA I or II. It represents an improvement in symptoms from being almost bedbound and unable to walk to experiencing only mild symptoms with limited or no symptoms during ordinary physical activity (walking, climbing stairs). The most reliable results for the population of interest in this review are reported as a range (due to data from more than one study which was too heterogeneous to be pooled). At 6 months after device implantation, 80-82% of subjects had achieved NYHA I/II. This proportion was similar (80-81%) at 2 years after device implant (Boothroyd et al 2013). There is weak evidence that a large proportion of recipients who are alive at 6 months and at 2 years achieve NYHA class I or II, from an initial NYHA IV health state. These results should be treated with caution as the two studies that they were based on were relatively small; one was controlled, but against an out of scope device; the other was uncontrolled. Results were based on observation of the 'as treated' population.
5	Quality of Life (Improvement in	A	The EQ5D is a measure of quality of life based on 5 dimensions:

	EQ-5D)		activities, anxiety, mobility, pain and self-care. A higher score indicates a better quality of life with a visual acuity scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). Across all three age groups (>70 years, 60-69 years and <60 years) there was a mean improvement of between 33 and 35 points between baseline and 12 months post implant. The mean 33-35 point change is significant and given the five dimensions of the EQ5D, this is likely to lead to practical and functional improvements. However, these results were based on retrospective, observational data from the INTERMACS registry and may not be generalisable as the registry excludes some patients, including those that did not survive implantation, those taking part in clinical trials and those that did not have baseline EQ5D scores recorded. The results should be treated with caution
6	Length of stay	B	The median length of stay in hospital after implantation with a VAD device was 22.5 days. This indicates that the procedure costs of implantation are likely to be significant, in addition to the device cost and longer term health care still required. This was based on one, small, retrospective, observed registry study of 176 VAD recipients as destination therapy. We do not know how this compares with similar patients who receive ordinary medical management and

			the number of days they need to be in hospital for symptom management.
7	Bleeding	A	Bleeding was the most commonly reported adverse event. The most relevant study of bleeding was from Jorde et al (2014) who followed up all 247 VAD recipients for at least 2 years after implantation. (Boyle et al (2014) included only post discharge patients, which may lead to incomplete reporting of adverse events). After two years follow up, 54% of the 247 VAD recipients experienced bleeding sufficient to require a blood transfusion. 13% of the VAD recipients required readmission to hospital and further surgical re-exploration. A significant proportion of VAD recipients experienced at least one severe bleeding adverse event (sufficient to require surgical exploration or a blood transfusion) during months 0-24 post implant. . Health care resources are likely to be required to manage these events. This was a well-conducted, prospective, observational, multicentre study of consecutive recipients of VAD in the USA. However, because there is no ordinary medical management control, there remains uncertainty about how this compares to people treated with ordinary medical management.
8	Neurological event (Stroke	A	Neurological events are commonly reported adverse events. It was reported as the proportion of patients who had a stroke, and as the number of events per patient

			year. The most reliable study which reported neurological events was the post approval, prospective observational study (n=247) (Jorde et al 2014). (Boyle et al (2014) included only post discharge patients, which may lead to incomplete reporting of adverse events). At 2 years post implantation, 11.7% of VAD recipients had experienced a stroke (0.083 strokes per patient year). There is no information about the severity of stroke, or about the proportion of people who had a stroke who recovered. This was a well-conducted, prospective, observational, multicentre study of consecutive recipients of VAD in the USA. However, there is no ordinary medical management control arm and we do not know how this compares to people treated with ordinary medical management.
9	Infection	A	Infections are a common reported adverse event for recipients of VAD devices. They are usually categorised as local non-device related infections, device related infections and sepsis. It was reported as the proportion of patients who had an infection and the number of events per patient year. The most reliable study which reported infection events was the post approval, prospective observational study (n=247) (Jorde et al 2014). At 2 years post implantation, 39% of VAD recipients had experienced a local non-device related infection (0.59 infections per patient year), 19% had had a device related

			infection (0.22 infections per patient year) and 19% had had sepsis (0.18 infections per patient year). The chance of having an infection is high although it is not known if the severity of the infections or the consequences of these reported adverse events (such as explantation or hospitalisation. This was a well-conducted, prospective, observational, multicentre study of 247 consecutive VAD recipients in the USA. However, there is no ordinary medical management control arm and it is not known how this compares to people treated with ordinary medical management.
10	Device Malfunction – thrombosis requiring exchange	A	Thrombosis occurs when there is clotting of blood cells in the device. It requires explantation of the implanted device, and implantation of new device. After two years follow up, 3.6% (0.027 events per patient year) of 247 VAD recipients experienced device related thrombosis which required exchange of the device (Jorde et al 2014). This is a highly undesirable and serious adverse event as device exchange requires significant resource (both financially and in terms of bed days) as well as exposing the recipient to significant post-operative risk and 30 day mortality. People treated with ordinary medical management would not be exposed to this risk. This was a well-conducted, prospective, observational, multicentre study of 247 consecutive recipients of VAD in the

			USA, and is generalisable to a UK setting.
11	Right Heart failure- inotropic support	A	A known consequence of left ventricular circulatory support is the development of right ventricular heart failure. This may require inotropic support (advanced drug treatment for heart failure). It was reported as the proportion of patients who had right heart failure requiring inotropic support and the number of events per patient year. The most reliable study which reported this adverse event was the post approval, prospective observational study (n=247) (Jorde et al 2014). At 2 years post implantation, 18% of VAD recipients had experienced right heart failure requiring inotropic therapy. This equated to 0.16 new events per patient year), Although the development of right heart ilaure is not the most common adverse event, it is a serious adverse event which affects the ability of the patient to benefit from the VAD, and may eventually lead to implantation of another device, if the response to inotropes is insufficient. This was a well-conducted, prospective, observational, multicentre study of consecutive recipients of VAD in the USA. However, there is no ordinary medical management control arm and it is not known if people treated with ordinary medical management also develop right heart failure requiring treatment.
12	Renal failure	A	Renal failure/dysfunction occurs when the kidneys no longer work effectively to filter and clean blood,

			causing unsafe levels of waste products to build up and without treatment, this can cause death. After two years follow up, 18% (0.15 events per patient year) of VAD recipients developed renal failure (Jorde et al 2014). The development of renal dysfunction post device implant is a serious adverse event which requires treatment of the cause (e.g. medicines for high or low blood pressure) and dialysis for a short time. If untreated, chronic renal failure can lead to end stage kidney diseases, requiring dialysis and eventually a kidney transplant. This result should be treated with caution. It is not known what proportion of patients treated with ordinary medical management experience renal failure. This was a well-conducted, prospective, controlled, multicentre study of 247 consecutive recipients of VAD in the USA, and the incidence of this adverse event is likely to be generalisable to a UK setting.
13	Re-hospitalisation	B	The hospital readmission rate was 1.77 events per patient year, for recipients of devices as DT, highlighting that complications associated with an implanted VAD commonly require readmission. The most common reasons for readmission were bleeding including gastrointestinal bleeding, infection and neurological events. Rehospitalisation is an important indicator of severity of an adverse event, and contributes significantly to the overall costs associated with survival with a VAD.

			This was based on one, small, retrospective, observed registry study of 176 VAD recipients as destination therapy. It is not known how this compares with similar patients who receive ordinary medical management.
14	Cost effectiveness	B	Cost effectiveness is expressed as the incremental cost effectiveness ratio (ICER) for a treatment (VAD) against a comparator (ordinary medical management). The ICER is a composite measure of both the life years gained with each treatment and the quality of life for those years. Typically, the National Institute for Health and Care Excellence (NICE) considers an ICER of less than £50,000 per QALY to be cost effective and affordable for 'end of life' care. Candidates for VAD have heart failure severe enough to meet the 'end of life' criteria. The estimated incremental cost effectiveness ratio over the projected lifetime (5 years) ranges from £91,299 to £162,388 [1]per quality adjusted life year (QALY). None of the modelled ICER estimates were more reliable than any other. The ICER range reflected a wide range of assumptions about the likely QALYs gained (1.5 to 2.83). This arose because the models were based on studies with a maximum follow up of two years, and assumptions were made about the additional life years and the quality of life for the remaining duration. The incidence of adverse events reduces the quality of the life years gained and increases the

[1] Based on conversion of euros and US dollars to GBP using currency exchange rates on 27 April 2017

			ICER. These results should be treated with caution. The studies used as the basis of the models were observational studies with no ordinary medical management comparator. In addition, the modelling of life years gained, adverse events and quality of life beyond the trial period introduces significant uncertainty. None of the cost effectiveness models were based in a UK setting and the results may not be generalisable to the NHS in England: the ICER (from an NHS payer perspective) may be different to Canada and the Netherlands, even though these most closely align with the NHS health care system. Despite the uncertainty about the ICER for VAD, even the most optimistic estimate is 2 times higher than that usually accepted by NICE.