National Institute for Health and Care Excellence

IP1292 Cardiac contractility modulation device implantation for heart failure

IPAC 11/04/19

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company Impulse Dynamics	1.1	**IPAC Consultation Document IP1292 - Cardiac contractility modulation device implantation for heart failure - Response from Impulse Dynamics.** Introduction Impulse Dynamics has completed its review of the IPAC Consultation Document IP1292 and would like to offer these comments for further consideration by the committee. We understand that the goals of the IPAC review are to provide objective evidence for the safety and efficacy of a particular therapy. In this case, the therapy is cardiac contractility modulation (CCM). With respect to safety of CCM, we agree that safety has been consistently demonstrated throughout its entire development path. Indeed, safety has been demonstrated with the Optimizer System in multiple clinical trials involving over 1,500 patients. Therefore, we will not discuss safety further in this document responding to IPAC consultation comments but rather will focus on the question of efficacy.	Thank you for your comment. Consultee agrees that the evidence on cardiac contractility modulation device implantation for heart failure raises no major safety concerns.
2	Consultee 1 Company Impulse Dynamics	1.1	The IPAC committee comments stated that the committee believed the efficacy data supporting CCM therapy was weak and did not support clinical implementation of the therapy. However, in our review of the consultation document, we have observed that the committee is basing their assessment on the overall population of heart failure patients including those with markedly reduced ejection fractions (LVEF of <25%). Through our many studies, we have been able to identify the cohort of patients that benefit the most from CCM therapy. These are patients with LVEF between 25-45% inclusive, NYHA Class III and ineligible for CRT. Our most recent evidence showing both safety and efficacy[i,ii] has been obtained in patients fitting these criteria. In our MTEP notification we have specified that this is the patient subgroup that the notification should be focused on. We are therefore only seeking	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

approval from IPAC for CCM therapy in this same discrete population of heart failure patients. Limiting the application of CCM therapy to a focused group of patients enhances the ability of the therapy to achieve its maximum effectiveness. We believe that the committee, therefore, should adjust its conclusions to this perspective.

As summarized in the Table below, results of clinical studies show that CCM improves VO2, NYHA and MLWHFQ and reduces CV mortality and hospitalizations. Please note that all of this work was done in the patient population we identified as deriving the most benefit from CCM therapy and is the patient population for which we are specifically seeking approval. Also note that the data included in these studies have been monitored and adjudicated. Further, additional publications provided in the original submission also show that LVEF increased in both long-term registries and in a short-term (6 month) study that employed 3D echocardiography.

Benefit	**Results**	**Indication or Population**	**Reference / Hyperlink**
Improvement in NYHA class, Increase vs. control	>80% of patient improving by 1 class; 40% improving by 2 classes	Heart Failure patients with symptoms despite OMT, NYHA II-IV, normal QRS, LVEF >25%.	**Abraham et al** JACC:HF, 2018, DOI: 10.1016/j.jchf.2018.04.010 **Anker et al** EJHF 2019 Jan 16 DOI 10.1002/ejhf.1374
Improvement in Quality of Life as measured by MLWHFQ, Increase vs. control	>11 points improvement	Heart Failure patients with symptoms despite OMT, NYHA II-IV, normal QRS, LVEF >25%.	**Abraham et al** JACC:HF, 2018, DOI: 10.1016/j.jchf.2018.04.010 **Anker et al** EJHF 2019 Jan 16 DOI 10.1002/ejhf.1374
Improvement in Peak VO_2, Increase vs. control	Improvement of 0.84ml/kgr/min	Heart Failure patients with symptoms despite OMT, NYHA II-IV, normal QRS, LVEF >25%.	**Abraham et al** JACC:HF, 2018, DOI: 10.1016/j.jchf.2018.04.010
Reduction in CV death and HF hospitalizations Increase vs. control	56% reduction vs. control	Heart Failure patients with symptoms despite OMT, NYHA III-IV, normal QRS.	**Abraham et al** JACC:HF, 2018, DOI: 10.1016/j.jchf.2018.04.010

The studies by Abraham et al., Anker et al. and Müller et al. are included in table 2 of the overview.

The studies by Kuschyk et al. and Yu et al. are included in table 2 of the overview.

The IP programme does not assess the efficacy and safety of comparator interventions.

Long term improvement in Left Ventricular Ejection Fraction (LVEF), Increase vs. baseline	3% points increase in 3D echo; >5% points increase in long term registries	Heart Failure patients with symptoms despite OMT, NYHA II-IV, normal QRS.	**Anker et al** EJHF 2019 Jan 16 DOI: 10.1002/ejhf.1374 **Mueller et al** Clin Res Cardiol, DOI: 10.1007/s00392-017-1135-9 **Kuschyk et al** Int J Card 2015; 183:76-81 DOI: 10.1016/j.ijcard.2014.12.178 **Yu el al** JACC Card Img 2009; 2(12):1341-9 DOI: **10.1016/j.jcmg.2009.07.011**

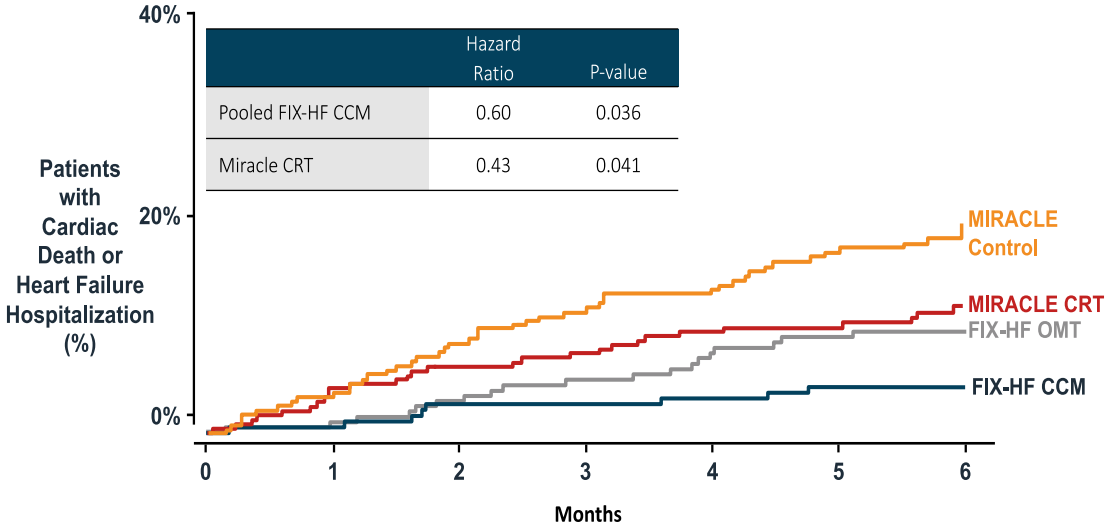
Comparisons with CRT

We would like to further point out to the committee that the data showing the efficacy of CCM therapy are similar to those available for CRT. The table below compares the effects of CCM with regard to the important endpoints to those obtained with CRT.

Parameter	CCM*	CCM 35%+*	CRT**
Exercise Tolerance ($pVO_{2)}$	0.84	1.76	0.91
Quality of Life (MLWHFQ)	-11.4	-14.9	-9.5
Functional Status (NYHA 1 class improvement)	81%	82%	70%
Walking Distance (6MW)	24.6	57.1	20.0

* All results statistically significant at the p=0.05 level or higher

**Weighted average by number of patients from: Higgins JACC 2003, Abraham NEJM 2002, Abraham Circulation 2004, Young JAMA 2003, Caseau NEJM 2001, Leclercq EHJ 2002

			Moreover, CV death and HF hospitalization shows improvement with CCM at a rate that is similar to that which has been shown in the MIRACLE study of CRT.  	
3	Consultee 1 Company Impulse Dynamics	1.1	<u>External Support for Efficacy</u> Finally, the efficacy of CCM therapy has been recognized by external experts. Indeed, CCM therapy is referenced in the EU Heart Failure Guidelines . Additionally, an expert advisory committee of the US FDA reviewed the Optimizer data and voted 12-0 in favor of the risk benefit ratio of the CCM therapy .	Thank you for your comment. The European Society of Cardiology guidelines (2016) state: 'CCM has been evaluated in patients with HFrEF in NYHA Classes II–III with normal QRS duration (<120 ms). An individual patient

				data meta-analysis demonstrated an improvement in exercise tolerance (peak VO_2) and quality of life (Minnesota Living with Heart Failure questionnaire). Thus CCM may be considered in selected patients with HF. The effect of CCM on HF morbidity and mortality remains to be established.' This has been added to the overview appendix.
4	Consultee 3 Specialist Society British Society for Heart Failure	1.1	Thank you for asking the British Society for Heart Failure (BSH) for our opinion on the NICE Interventional procedures consultation document on Cardiac contractility modulation (CCM) device implantation for heart failure [IPG10106]. We agree with NICE in their draft recommendations. We concur that there is a major lack in evidence supporting the efficacy of CCM (and no studies which report an improvement in mortality), and that studies to date have been of low quality and with findings potentially subject to significant bias. Although this CE-marked device is implanted in certain European counties (including Germany and Austria), the 2016 ESC heart failure guidelines[1] stated: "Currently, the evidence is considered insufficient to support specific guideline recommendations for other therapeutic technologies,	Thank you for your comment. Consultee agrees with main recommendations.

			including …. cardiac contractility modulation; further research is required". CCM is still considered "investigational" in the USA. The recently published FIX-HF-5C study[2] was a small, prospective, randomized study of optimal medical therapy (OMT) alone versus OMT plus CCM in patients with medically refractory, but ambulatory, heart failure (NYHA functional class III or IV) with EF ranging from 25% to 45%. Only 68 of the 74 subjects assigned to the CCM treatment group underwent device implantation. The primary endpoint (at a follow up of 24-weeks) was only reached when extra subjects were "borrowed" from a previous study (FIX-HF-5) and only then was there a modest improvement in peak VO_2 shown (0.84 (0.123 to 1.552) ml/kg/min. Therefore, this finding is of uncertain clinical benefit. Furthermore, although this study achieved its primary safety endpoint there were 7 complications in 68 subjects (complication rate 10.3%). A further study, IMPULSE-HF[3] was terminated due to slow recruitment. In summary, the BSH agrees with the findings of NICE on Cardiac Contraction Modulation. We feel this device has no current role in the routine management of heart failure patients, but we would welcome further research in this area. 1. Ponikowski P et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. doi:10.1093/eurheartj/ehw128 2. Abraham WT et al. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. J Am Coll Cardiol HF. 2018;6:874–83 3. Cardiac Contractility Modulation Therapy in Subjects With Medically Refractory Heart Failure; NCT02857309	
5	Consultee 1 Company Impulse Dynamics	General	<u>Additional considerations</u> During the committee's discussion of the efficacy of CCM therapy, some issues arose that deserve further comment. Ventilatory Anaerobic Threshold (VAT) was noted to be an endpoint for the randomized FIX-HF-5 trial of 428 patients and did not attain statistical significance in the main cohort of the study. Importantly, it should be noted that in patients with EF > 25% subgroup that we are seeking approval for, there were statistically significant improvements in VAT demonstrated (0.64 ml/kgr/min, p=0.03). The committee postulated that a "placebo" effect might have influenced the results of studies supporting the efficacy of CCM therapy. We contend that there was not such an effect in play in	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

			the timeline of measurement (6-12 months). In the FIX-CHF-4 study[iii], which was a randomized double blind, cross-over trial of the safety and efficacy of CCM therapy for 3 months, demonstrated no sustained placebo effect after the first 2-3 months and certainly showed the efficacy of CCM in this relatively short timeline of action. Additionally, we observed a reduction in CV death and HF hospitalizations in 2 randomized studies, as well as a reduction in the rate of HF hospitalizations the year following initiation of CCM treatment versus the year prior to CCM therapy in a multicenter registry. All these findings further support the robustness of the effect that is not influenced by placebo.	
6	Consultee 1 Company Impulse Dynamics	General	Finally, during the IPAC meeting on January 10th, the committee discussed the issue of the duration of CCM therapy. The FIX-HF-13 study[iv] compared 5 hours of CCM therapy to 12 hours of CCM therapy in patients with moderate to severe heart failure. Symptoms, quality of life and exercise tolerance were assessed in a double-blind fashion. The results demonstrated that all parameters improved with CCM therapy but there was no discernible difference between the improvements shown with 5 vs. 12 hours per day of therapy. We have concluded in our own dose-response studies that CCM therapy should be targeted at 5 hours delivery per day.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
7	Consultee 1 Company Impulse Dynamics	General	Conclusion According to the ESC HF guidelines, among the goals of treatment in patients with HF are to improve their clinical status, functional capacity and quality of life and prevent hospital admissions. CCM therapy has shown in convincing, large, multiple studies that it meets each one of these goals. CCM compares favourably to other modalities previously developed that are now established therapies in CHF. The Optimizer device has been piloted in the UK in 2018 by the cardiology team at Eastbourne District General Hospital and we hope that feedback has been sought from both the patients and clinical team involved. We believe that CCM therapy should be made available under standard arrangements to UK heart failure patients with EF 25-45%, NYHA Class III and ineligible for CRT. Currently these patients have no alternative treatment option other than to continue on Optimal Medical Treatment which is not providing symptomatic relief. References Abraham et al, A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation JACC Heart Fail. 2018 Oct;6(10):874-883	Thank you for your comment. A specialist adviser questionnaire was received from a consultant cardiologist who has done the procedure. The studies by Abraham et al., Anker et al. and Borggrefe et al. are included in table 2 of the overview.

			Anker et al, Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction, Eur J Heart Failure 2019 doi:10.1002/ejhf.1374 European Heart Journal (2016) 37, 2129–2200 doi:10.1093/eurheartj/ehw128 section 8.3, p. 2157 Available in: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM627851.pdf Borggrefe, M.M., et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. Eur Heart J 29, 1019-1028 European Heart Journal (2016) 37, 2129–2200 doi:10.1093/eurheartj/ehw128 section 8.3, p. 2147	
8	Consultee 1 Company Impulse Dynamics	3.2	CCM Efficacy With respect to efficacy, the committee has chosen VO2, NYHA Class, MLWHFQ and LVEF as appropriate measures. We agree that these parameters are appropriate measures of efficacy for CCM therapy. We would also like to point out that data related to the rate of hospitalizations to be a robust indicator of efficacy and we would like to include this index in the discussion.	Thank you for your comment. Rate of hospitalisation has been added to the key efficacy outcomes listed in section 3.2 of the guidance.
9	Consultee 2 Patient	General	My observations are that due to the lack of single/double-blind RCT evidence and maybe the suitability/relatability of the evidence to the UK NHS there are concerns around the efficacy. I completely understand this, however, there are large subgroups of people living with HF who may benefit from MEDTECH devices that struggle to demonstrate value through the NICE assessment system and therefore never have the chance to become a therapy option. As a note and a point on record. To ensure MEDTECH companies of all sizes have an opportunity to design and deliver trials that do tick the boxes of the rigorous expectations of reviewers, we need to look at designing a system that embraces the needs of patients in a very needed area of HF and make available funding to assist in producing trials that do deliver outcomes that we need to make fair and uncompromised decisions around MEDTECH in HF.	Thank you for your comment.

10	Consultee 2 Patient	Data protection checkbox	Reference your checkbox on data protection it is out of date and should relate to GDPR not an out of date act. See below.	Thank you for your comment. This will be changed.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."