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Medical Policy

Subject:	**Cardiac Contractility Modulation Therapy**		
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Description/Scope

This document addresses the use of cardiac contractility modulation therapy designed to treat chronic moderate-to-severe heart failure.

Note: Please see the following related document for additional information:

- **CG-SURG-63 Cardiac Resynchronization Therapy with or without an Implantable Cardioverter Defibrillator for the Treatment of Heart Failure**

Position Statement

Investigational and Not Medically Necessary:

The use of cardiac contractility modulation therapy is considered investigational and not medically necessary for all indications, including but not limited to heart failure.

Rationale

On March 21, 2019 the U.S. Food and Drug Administration (FDA) granted Impulse Dynamics breakthrough device exemption for the OPTIMIZER® Smart Implantable Pulse Generator (Impulse Dynamics, Orangeburg, NY), with approved use in the treatment of individuals with chronic, moderate-to-severe (New York Heart Failure [NYHA] Class III or ambulatory Class IV) heart failure (HF) who remain symptomatic despite guideline directed medical therapy (GDMT). Recipients must be in normal sinus rhythm with left ventricular ejection fraction (LVEF) from 25 to 45 percent and not considered a candidate for cardiac resynchronization therapy (CRT) to restore normal heart rhythm. The OPTIMIZER Smart System treatment, referred to as cardiac contractility modulation (CCM), delivers electrical signals to the ventricles

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during the ventricular absolute refractory period. The expected result is improvement in 6-mintue hall walking distance, quality of life, functional status, and exercise tolerance. (Product Label Information, 2019)

The original technology for CCM was developed by Impulse Dynamics. The original device was evaluated in a trial by the FDA that did not demonstrate efficacy. The original study used a broader group of HF participants and endpoints that were difficult to achieve in the clinical trial. Ultimately, the trial failed, but subgroup analysis showed which participants could possibly benefit from use of the device.

The *FIX-HF-5 study* was a prospective, unblinded, randomized study comparing CCM plus optimal medical treatment (OMT) to OMT alone in 428 participants. Subjects had NYHA functional class III or IV HF with ejection fraction (EF) of ≤ 45%. (Abraham, 2015). The FIX-HF-5 study met its primary safety end point, but did not reach its primary efficacy end point; changes in ventilatory anaerobic threshold (VAT) of responders. However, significant improvements in primary and secondary efficacy endpoints, including the responders VAT endpoint, were met in a prespecified subgroup analysis of individuals with EFs ranging from 25%-45% (n=221; p=0.001). Based on the subgroup analysis a new, prospective study was designed and described to confirm the efficacy of CCM in this population.

Abraham and colleagues (2018) reported results from the *FIX-HF-5C* confirmatory study (NCT01381172) to prospectively test the efficacy and safety of CCM in participants with NYHA functional class III or IV symptoms and EF 25-45%. A total of 160 participants were randomized to continue OMT (n=86) or CCM (treatment, n=74, unblinded) for 24 weeks. The primary efficacy endpoint was met with a peak Vo_2 between groups of 0.84 (95% Bayesian credible interval: 0.123 to 1.552) ml O2/kg/min. The following secondary outcomes, Minnesota Living With Heart Failure questionnaire (p<0.001), NYHA functional class (p<0.001), and 6-min hall walk (p=0.02), were all significantly better in the treatment group compared to the control group. Of the 68 (n=68/74 underwent implant in the treatment group) individuals implanted with the OPTIMIZER device, there were seven device-related events reported. There was a reduction in the composite of cardiovascular death and HF hospitalizations from 10.8% to 2.9% (p=0.048). There was one death related to sepsis at 164 days after device implantation in the treatment group following surgery for an incarcerated hernia. Long-term risks of infection cannot be known at this time.

The FDA approval of the OPTIMIZER Smart System is based on preliminary findings reported of 389 participants with moderate-to-severe HF (*FIX-HF-5 subgroup*, n=229; *FIX-HF-5C*, n=160) from two randomized, multi-center clinical trials that have not been published in a peer-reviewed journal. Participants received OMT alone versus OMT plus implantation with an OPTIMIZER Smart System. Study inclusion

criteria were NYHA function class III or ambulatory class IV with HF despite OMT, an EF ranging from 25-45% as determined by echocardiographic core laboratory, and normal sinus rhythm with QRS duration < 130 ms. Individuals who had an EF ≤ 35% were required to have an ICD unless there were extenuating circumstances. The primary effectiveness endpoint was met, with estimated mean difference in peak Vo_2 at 24 weeks between the CCM groups and control groups of 0.84 mL/kg/min with a Bayesian credible interval of (0.12, 1.55) mL/kg/min. "The probability that CCM is superior to control was 0.989, which exceeds the 0.975 criterion required for statistical significance of the primary endpoint." Among the pooled data 60.1% (104/173) of participants in the CCM group and 34.9% (59/169) in the control group achieved ≥ 1 class improvement in NYHA at 24-week follow up period. At the 24-week follow-up, the change in Quality of Life measured by the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) total score between the groups in the pooled data, was -10.9 (95% confidence interval [CI]; -14.6, -7.2). The primary safety endpoint was met. "The complication-free proportion in the CCM group cohort was 89.7% (61/68) with lower confidence limit of 79.9% (one-sided alpha=0.025), which was greater than the pre-defined threshold of 70%. The majority of complications (5/7, 71.4%) were lead dislodgements." Among the OPTIMIZER group and the control group, the freedom from death (98.3%, 95.3%; p=0.2549), cardiovascular death (100%, 96.5%; p=0.1198), composite rate of all-cause death or all-cause hospitalizations (78.1%, 77.7%; p=0.9437) and overall rate of AEs and SAEs were similar at 24-weeks. (Product Label Information, 2019)

According to the FDA Summary of Safety and Effectiveness Data (SSED) the FDA concluded that:

> **Even though the primary effectiveness endpoint (change in peak V02) met its pre-specified endpoint the clinical significance was questioned; primarily because the observed treatment difference was due to a decline from baseline in the control arm. The treatment arm, depending on analysis method, either showed a decline in peak Vo_2 or a marginal increase; making claims of increased exercise tolerance not justifiable.**
>
> **Two subjective endpoints, Quality of life per the MLWHFQ, and the 6 minute hall walk, did show an improvement. However, the confidence intervals were somewhat wide; possibly due to the relatively small sample size and unblinded nature of the trial (control group did not receive a device). The latter raised the question among panel members if the positive outcomes for the subjective endpoints could be due to a placebo effect.**

The 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America Focused update of the 2013 American College of Cardiology Foundation (ACCF)/American Heart

Association (AHA) Guideline for the Management of Heart Failure does not address use of the use of cardiac contractility modulation therapy as a treatment for HF (Yancy, 2017).

In summary, the current evidence base is insufficient to support the use of CCM therapy with the OPTIMIZER Smart System in individuals with chronic, moderate-to-severe HF. The current studies included relatively small sample size with short follow-up duration, therefore the long-term complications such as infection and lead fractures are unknown. Longer studies with longer and more representative populations are needed to confirm longer-term effects of CCM therapy on whether health outcomes are significantly improved relative to standard of care for HF management.

The OPTIMIZER Smart System is being studied in an ongoing prospective, multicenter, post approval study. The study is designed to evaluate the long-term safety and efficacy of the device as well as to rule out placebo effects and more precisely identify the group of individuals that most benefit from the device.

Background/Overview

According to the Centers for Disease Control (CDC) and Prevention nearly 5.7 million Americans are currently diagnosed with HF, and more than 915,000 new cases are diagnosed each year (CDC, 2019). Approximately 50% of individuals with HF die within 5 years of diagnosis. As a result of HF, the weakened heart muscle causes inadequate filling of the left ventricle, as well as a backflow of blood into the left atrium, both resulting in decreased cardiac output and increased symptoms for the afflicted individual. Symptoms can include shortness of breath, fatigue, swelling in the ankles, feet, legs, abdomen and veins in the neck. Currently there is no cure for HF; medical therapy includes a combination of diuretics, digoxin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-blockers, and aldosterone antagonists. Some individuals may remain symptomatic, despite medical therapy. Ongoing studies evaluate other treatment options to assist physicians in the management of individuals with severe HF.

Definitions

Bayesian hierarchical analysis: A statistical method providing estimates of post-analysis parameters based on frequencies observed in a prior analysis evaluated in a series of hierarchical models.

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Guideline-directed medical therapy (GDMT): This term was adopted by the writing groups for the major specialty medical societies, (such as found in Tracy, 2012 and Yancy, 2013) in 2012; the term replaces and is synonymous with "Optimal medical therapy."

Heart failure: A condition in which the heart no longer adequately functions as a pump. As blood flow out of the heart slows, blood returning to the heart through the veins backs up, causing congestion in the lungs and other organs.

New York Heart Association (NYHA) Definitions: The NYHA classification of heart failure is a 4-tier system that categorizes subjects based on subjective impression of the degree of functional compromise; the four NYHA functional classes are as follows:

- **Class I - patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain; symptoms only occur on severe exertion.**
- **Class II - patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity (e.g., moderate physical exertion such as carrying shopping bags up several flights of stairs) results in fatigue, palpitation, dyspnea, or anginal pain.**
- **Class III - patients with cardiac disease resulting in marked limitation of physical activity; they are comfortable at rest; less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.**
- **Class IV - patients with cardiac disease resulting in inability to carry on any physical activity without discomfort; symptoms of heart failure or the anginal syndrome may be present even at rest; if any physical activity is undertaken, discomfort is increased.**

Ventilatory Anaerobic Threshold (VAT): The point in exercise testing at which anaerobic metabolism is detected by comparing oxygen consumption with CO2 production. VAT provides a measure of exercise capacity that has prognostic value for individuals with heart failure

Vo_2: Oxygen uptake. This can be calculated using the Fick Equation (Vo_2 = [SV x HR] x [CaO2 - CvO2]) in which oxygen uptake equals stroke volume times the heart rate times the difference in oxygen concentration between arterial and venous blood. Vo_2 indicates functional aerobic capacity is widely used as a measure of cardiorespiratory fitness.

Coding

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The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
0408T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator
0417T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent

	programmed values with analysis, including review and report, implantable cardiac contractility modulation system
0418T	**Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system**

ICD-10 Procedure

02H63MZ	**Insertion of cardiac lead into right atrium, percutaneous approach [when specified as a lead for a contractility modulation device]**
02HK3MZ	**Insertion of cardiac lead into right ventricle, percutaneous approach [when specified as a lead for a contractility modulation device]**
0JH60AZ	**Insertion of contractility modulation device into chest subcutaneous tissue and fascia, open approach**
0JH63AZ	**Insertion of contractility modulation device into chest subcutaneous tissue and fascia, percutaneous approach**
0JH80AZ	**Insertion of contractility modulation device into abdomen subcutaneous tissue and fascia, open approach**
0JH83AZ	**Insertion of contractility modulation device into abdomen subcutaneous tissue and fascia, percutaneous approach**

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. **Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. JACC Heart Fail. 2018; 6(10):874-883.**
2. **Abraham WT, Lindenfeld J, Reddy VY, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with moderately reduced left ventricular ejection fraction and a narrow QRS duration: study rationale and design. J Card Fail. 2015; 21(1):16-23.**
3. **Kadish A, Nademanee K, Volosin K, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. Am Heart J. 2011; 161(2):329-337.**

4. **Kloppe A1, Mijic D, Schiedat F, et al. A randomized comparison of 5 versus 12 hours per day of cardiac contractility modulation treatment for heart failure patients: A preliminary report. Cardiol J. 2016; 23(1):114-119.**
5. **Müller D, Remppis A, Schauerte P, et al. Clinical effects of long-term cardiac contractility modulation (CCM) in subjects with heart failure caused by left ventricular systolic dysfunction. Clinical Research in Cardiology. 2017; 106(11):893-904.**
6. **Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilator response to exercise in patients with chronic heart failure and preserved exercise tolerance: maker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation. 2001; 103(7):967-972.**

Government Agency, Medical Society, and Other Authoritative Publications:

1. **Impulse Dynamics. Continued Access Protocol for the evaluation of the OPTIMIZER Smart System (FIX-HF-5CA). NLM Identifier: NCT03102437. Last updated April~~January~~ 2~~6~~1, 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03102437?term=OPTIMIZER+Smart+system&cond=heart+failure&rank=2. Accessed on June~~April~~ 10, 2019.**
2. **Impulse Dynamics. Evaluation of the safety and efficacy of the 2-lead OPTMIZER® Smart System (FIX-HF-5C2). NLM Identifier: NCT03339310. Last updated December 7, 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT03339310?term=OPTIMIZER+Smart+system&cond=heart+failure&rank=1. Accessed on April 10, 2019.**
3. **Mozaffarian D, Benjamin EJ, Go AS, et al. AHA Statistical Update. Heart disease and stroke statistics – 2016 update a report from the American Heart Association. Circulation. 2015; 133:e38-e360.**
4. **Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2012; 60(14):1297-1313.**
5. **U.S. Food and Drug Administration (FDA). Pre Market Approval (PMA). Medical Devices. OPTIMIZER Smart System – No. P180036. Rockville, MD: FDA. March 21, 2019. Available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm634106.htm. Accessed on April 10, 2019.**
6. **U.S. Food and Drug Administration (FDA) Premarket Notification Database. Implantable Pulse Generator, OPTIMIZER Smart System. Summary of Safety and Effectiveness Data (SSED). No. P180036. Rockville, MD: FDA. March 21, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180036b.pdf. Accessed on April 24, 2019.**

7. **Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017; 70:776-803.**
8. **Yancy CW, Jessup M, Bozkurt B, et al. 2013ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013; 128:e240-e327.**

Websites for Additional Information

1. **Centers for Disease Control and Prevention. Heart failure fact sheet. Last updated January 8, 2019. Available at: https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_failure.htm. Accessed on April 10, 2019.**
2. **National Heart, Lung and Blood Institute. Heart failure. Available at: http://www.nhlbi.nih.gov/health/dci/Diseases/Hf/HF_WhatIs.html. Accessed on April 10, 2019.**

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	06/06/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

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