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Ms. Tamara Syrek Jensen, J.D.
Director, Coverage & Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard, C1-14-15
Baltimore, Maryland 21244

Dear Ms. Syrek Jensen:

Medtronic is the world's leading medical technology company, specializing in implantable and interventional therapies that alleviate pain, restore health, and extend life. We are committed to the continual research and development necessary to produce high-quality products and to support innovative therapies that improve patients' health outcomes.

We appreciate the opportunity to comment on the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting on heart failure. Medtronic appreciates CMS's interest in the relevant outcomes in studies for heart failure treatment technologies.

Medtronic has provided comments in response to the specific questions and discussion points that CMS posted in the MEDCAC Meeting notice. CMS specifically expressed "… medical technologies are receiving market authorization based on less long-term data with greater reliance upon intermediate and surrogate outcomes. As a result, assessments of medical technologies are being made with more frequent evidence gaps with respect to the clinically meaningful health outcomes for CMS beneficiaries."

Heart failure clinical trials with the traditional standard endpoints of mortality and morbidity are increasingly challenging to complete as event rates decline with the evolution of care and as we move toward studying healthier heart failure populations. These trials are exceedingly less feasible to conduct in a time and cost efficient manner. Mortality and morbidity as continued standards therefore, may delay or potentially reduce the availability of important heart failure innovations to patients who could benefit. We believe the aims of establishing safety and effectiveness of a therapy can confidently be assessed beyond traditional mortality and morbidity studies such that important innovations can be delivered in a timely manner to patients in need.

Medtronic presents consideration that there are important and reliable surrogate outcomes that should be considered as appropriate outcomes for heart failure treatment technologies. We highlight two viable surrogate outcomes to be considered.

Clinical Composite Score (CCS)

The Packer CCS was introduced in 2001 as a means to measure a HF intervention's intermediate effect on outcomes and symptoms. The CCS leverages clinically meaningful objective measures of death and HFH and subjective measures of NYHA functional class and global assessment. Importantly, CCS accounts for discontinuation of therapy due to clinical deterioration. The decision flow to identify whether the patient's status "improved," "worsened," or is "unchanged" is decided by a hierarchical flow, placing priority on death, HFH, crossovers, then subjective measures. Patient well-being is only relevant in the absence of outcomes or worsening NYHA class. Unlike other endpoints, every patient contributes to the analysis through the tested duration.

CCS has been used in notable trials as a primary endpoint[i,ii,iii] and a key secondary endpoint[iv v,vi,vii]and continues to be used[viii,ix]. The commonality of the endpoint enables comparative effectiveness research against new products[x]. A 2014 analysis of 1603 CRT patients from five trials shows six month CCS status to be predictive of long-term survival and healthcare utilization[xi].

Using CCS is likely to have a dramatic impact on the duration and cost efficiency of trial execution. In a review of nine pivotal CRT trials, the trials using CCS as a key endpoint were substantially shorter in duration (2.9 vs 4.7 yrs.) and 91% reduced in the patient-years sample compared to morbidity/mortality trials . Despite the smaller sample and shorter duration, to date we are unaware of an intervention showing a significant effect in CCS but not in mortality and morbidity outcomes (i.e. false positive). While REVERSE reported an insignificant CCS effect of CRT in select NYHA I-II patients at 12 months, the pre-specified endpoint only evaluated worsening vs non-worsening. When CCS was used conventionally, accounting also for unchanged and improved statuses, the effect was significant and at multiple time-points[xii]. CRT for mild HF would further prove effective in the reduction of outcomes one and two years later when reported by the MADIT CRT[xiii] and RAFT[xiv] trials, respectively.

There are some limitations to CCS worth noting. CCS may not detect a favorable effect after early worsening. However, this limitation also resides in other outcome measures. CCS was built as an intermediate measure, and its sensitivity at measuring long-term effect is unknown. Further, components of the CCS can be influenced by bias thus patient and clinician blinding may be needed.

Myocardial Remodeling

Myocardial remodeling has an important relationship to HF as injury to the myocardium can result in adverse ventricular remodeling, impairing contractile function, and reducing stroke volume. Remodeling increases patient risk of HF symptoms, morbidity, and mortality. HF drug therapy[xv] and CRT [xvi,xvii ,xviii,xix,xx,xxi] have been demonstrated to limit or reverse LV remodeling and improve long-term survival. LVESVi was a prospectively powered secondary endpoint in the REVERSE trial.

Thus far, although limited to post-hoc analyses, LVESV has been shown to be the strongest echo measure predictive of survival[xxii,xxiii,xxiv]. Change in myocardial function as a predictor of long-term outcomes in the context of a new HF intervention is biologically plausible and an objective measurement unlikely to be influenced by patient or clinician bias. This may be particularly appealing when blinded randomization coupled with long-term follow-up is unfeasible[xxv]. We estimate that half of the qualifying patients for the MIRACLE EF study declined participation due to the chance of having a sham device implant for five years. Systematic measurement of cardiac volumes allows for specific detection of improvement and worsening of HF function.

Identifying echocardiographic measures to predict patient response to CRT has been challenging, as poor agreement to clinical measures has been reported[xxvi]. Interpretation of results can be difficult for modest but statistically significant degrees of functional change. Additionally, linking remodeling to economic measures has yet to be established and further research is warranted. Remodeling measures, as a key intermediate endpoint[xxvii] or as a component of long-term measures[xxviii] has been useful and may continue to be, particularly when the intervention risks are well-known. For example, due to the established safety profile and robust evidence of CRT's effects on volumes in systolic dysfunction (i.e. EF ≤ 35%), volumes as a primary endpoint for patients with ejection fractions above 35% may be justified.

Thank you for your consideration of these recommendations. We look forward to the MEDCAC Meeting on Heart Failure outcome measures. Please do not hesitate to contact me about the information we have provided.

Sincerely,

Dan Schaber, PharmD
Vice President, Heart Failure Clinical Research
Medtronic, plc
Cardiac Rhythm and Heart Failure

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