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EDITORIAL COMMENT

The Need to Innovate and Accelerate Clinical Trial Performance

BeAT the Clock*

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The current era of health care innovation provides an opportunity to improve care of patients with heart failure (HF), a chronic disease with an unacceptable morbidity and mortality despite advancements in therapy. With rapid development of several novel drug therapies for HF, the toolbox for clinicians caring for affected patients is now even more full. However, even with excellent medical care, the prognosis of patients with heart failure with reduced ejection fraction (HFrEF) remains poor. Compounding this, a "ceiling" is being reached where medical therapies will be harder to deliver due to cost, care complexity, higher risk for drug-drug interactions, and side effects (1). A natural response might be to turn to device therapy in HFrEF. However, HF device studies are challenging. Device trials are unique because they are usually smaller than drug trials, are difficult to blind, randomize, and control, are occasionally operator dependent, have diverse endpoints, and device modifications may occur during the trial. To more rapidly deliver effective device therapies to patients with HFrEF, an entirely new approach to trial execution is needed.

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In this issue of the *Journal*, Zile et al. (2) report the results of a uniquely designed study, the BeAT-HF (Baroreflex Activation Therapy in Patients with Heart Failure and a Reduced Ejection Fraction) trial. This study examined the safety and efficacy of baroreflex activation therapy (BAT) in patients with HFrEF; the results of the study suggest BAT significantly improved efficacy measures of Minnesota Living with Heart Failure Questionnaire (MLWHF) score, increased 6-min hall walk (6MHW) distance, and decreased N-terminal pro B-type natriuretic peptide (NT-proBNP), with an acceptable safety profile (2).

Notably, despite the fact the efficacy measures are obviously not "hard" clinical endpoints, the U.S. Food and Drug Administration (FDA) granted approval for the device. The steps in the journey to approval are the most interesting piece of this story, and provide insight for investigators in future HF trials.

The FDA's Breakthrough Devices Program is part of the 21st Century Cures Act to stimulate drug and device development (3) and provides a pathway that would potentially accelerate market access for therapies intended to treat a life-threatening or irreversibly debilitating disease. This includes basing approval on intermediate endpoints without a reduction in morbidity or mortality necessarily, but with the expectation that such clinical reductions be pursued in ongoing studies (4). Specific to HF device trials, rather than grant approval based on mortality/HF hospitalization, approval might be initially based

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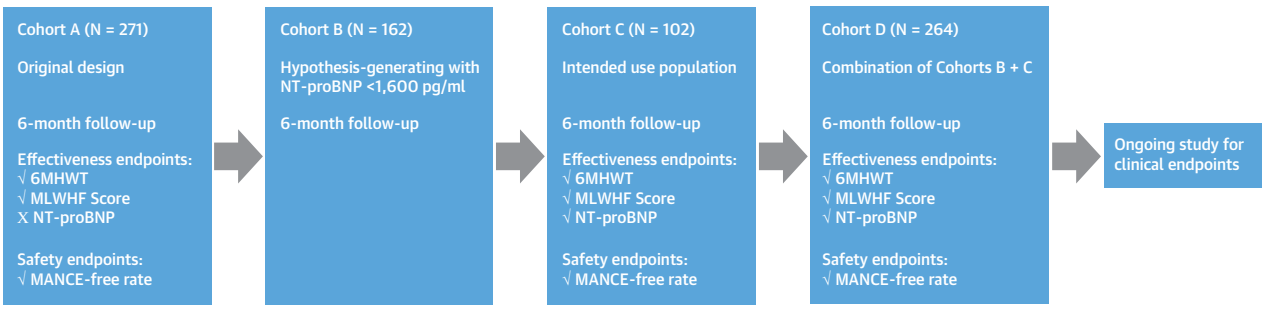
FIGURE 1 **Phases of the BeAT-HF Trial**



6MHW = 6-min hall walk; BeAT-HF = Baroreflex Activation Therapy in Patients with Heart Failure and a Reduced Ejection Fraction; MANCE = major adverse cardiovascular and neurological events; MLWHF = Minnesota Living with Heart Failure Questionnaire; NT-proBNP = N-terminal pro B-type natriuretic peptide.

on meeting several intermediate endpoints that support a meaningful clinical benefit (5). However, HF device trials should then use predictive modeling for longer-term outcomes of mortality/HF hospitalization. While it is important to know FDA requirements for an HF device approval, it is just as important to know Centers for Medicare and Medicaid Services (CMS) requirements for reimbursement for an HF device during trial design to ensure future coverage. CMS approvals are based on therapies that are medically necessary and reasonable (6), whereas FDA approval is based on whether a therapy is safe and effective (7).

With the FDA's focus on safety and efficacy, a seamless phased approach is suggested for device approval. In Phase 1 (the Expedited Phase), study subjects are randomized and evaluated for safety and endpoints relative to symptomatic improvement. Morbidity and mortality trends are noted and a premarket approval for the device can be requested and may be approved based on symptomatic improvement; a supplemental application would be needed for device changes or upgrades. Phase 2 (the Extended Phase) includes subjects from Phase 1, and analysis timing is dependent on enough morbidity and mortality data being collected on all subjects; if results are acceptable, an application to the CMS for approval and possibly to the FDA for additional labeling ensues.

The BeAT-HF trial design was created in a unique collaboration with the FDA under the Breakthrough Devices Program (**Figure 1**); in Phase 1, the effects of BAT on 6MHW, MLWHF questionnaire, and NT-proBNP at 6 months were examined. The safety endpoint for this Expedited Phase was major adverse cardiovascular and neurological events related to the system or the procedure in patients implanted with the BAT system (8). In the first cohort of patients with 6-month data available, improvements were seen in 2 of the 3 alternative endpoints, 6MHW and MLWHF quality of life, and the safety profile was acceptable. Notably, there was no significant reduction in NT-proBNP concentrations. This contrasted the significant reduction of NT-proBNP seen in the previously published Phase 2 trial (9). The investigators hypothesized that this may have been due to inclusion criteria of NT-proBNP ≥1,600 pg/ml in this Phase 3 trial resulting in the enrollment of patients who were "too sick" to derive benefit from BAT. This led to the creation of Cohort B, the intended use population, with the same enrollment criteria except it now included expectation of a baseline NT-proBNP <1,600 pg/ml. All 3 alternative endpoints were then met. Cohort C consisted of patients with the new enrollment criteria created to confirm findings of Cohort B. And finally, Cohort D consisted of study subjects in Cohorts B and C, the full intended use study population.

Based on results from Cohort D, BAT was approved by the FDA for improvement in symptoms in patients who are New York Heart Association functional class III or class II (with recent history of class III), have left ventricular ejection fraction ≤35%, and have NT-proBNP <1,600 pg/ml, excluding patients indicated for cardiac resynchronization therapy (2).

An important consideration raised by this trial is the use of an upper limit cut point for NT-proBNP inclusion criteria. Such practice is rare, even in drug trials (10), but may be a supportable strategy as the HF space inches toward using biomarkers and other tools to personalize care.

The interactive and adaptive design of BeAT-HF is groundbreaking. Given the inherent challenges of HF device trials, including cost and smaller size

compared to drug trials, such design and implementation of device trials should be encouraged in the future, with collaboration with the regulatory agencies. We would argue this approach should also be extended to drug therapies that have well-defined intermediate endpoints.

The current clinical trial cycle time for new therapies continue to increase, with pivotal trials taking an average of nearly 4 years to reach conclusion (11). In the pursuit of novel therapies, a disease with a high morbidity and mortality burden such as HF deserves upfront collaboration with regulatory agencies and payers to create, adapt, and complete studies in a timely fashion. The work of Zile et al. (2) provides proof of concept that this is possible, and should be a model for future efforts and extended to drug therapies as well. With growing incidence, prevalence, and risk of patients affected by HF, all hands must be on deck to "beat the clock" and get safe, effective treatments to our patients.

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