

# Development of Therapeutics for Heart Failure

## Exploring New Endpoints for Patients With Heart Failure With Preserved Ejection Fraction

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**Abstract**—The epidemiological, clinical, and societal implications of the heart failure (HF) epidemic cannot be overemphasized. Approximately half of all HF patients have HF with preserved ejection fraction (HFpEF). HFpEF is largely a syndrome of the elderly, and with aging of the population, the proportion of patients with HFpEF is expected to grow. Currently, there is no drug known to improve mortality or hospitalization risk for these patients. Besides mortality and hospitalization, it is imperative to realize that patients with HFpEF have significant impairment in their functional capacity and their quality of life on a daily basis, underscoring the need for these parameters to ideally be incorporated within a regulatory pathway for drug approval. Although attempts should continue to explore therapies to reduce the risk of mortality or hospitalization for these patients, efforts should also be directed to improve other patient-centric concerns, such as functional capacity and quality of life. To initiate a dialogue about the compelling need for and the challenges in developing such alternative endpoints for patients with HFpEF, the US Food and Drug Administration on November 12, 2015, facilitated a meeting represented by clinicians, academia, industry, and regulatory agencies. This document summarizes the discussion from this meeting.

**Key Words:** aging ■ drug approval ■ heart failure ■ hospitalization ■ quality of life

Patients with heart failure (HF) with preserved ejection fraction (HFpEF) comprise half of all HF patients.<sup>1</sup> These patients are older, have high comorbidity burden, and demonstrate significant pathophysiological heterogeneity.<sup>2</sup> No therapy has been shown to improve outcomes for these patients. This lack of efficacy may result from the gap between the

mechanism of action of drugs used as a standard of care in HF and the absence of clear understanding of the underlying disease and therapeutic targets in the specific conditions of HFpEF. The main reason may be related to the fact that the abnormalities causing signs and symptoms and progression of HFpEF were not targeted. It is possible that there are many

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HFpEF phenotypes that are not clearly understood, and one size does not fit all. Clearly, more work is needed to better dissect the pathophysiological mechanisms leading to HFpEF.

These patients also have substantially reduced functional capacity and quality of life (QoL) on a daily basis. Although mortality and hospitalization risk reduction remain important goals, it is imperative to explore interventions that impact endpoints that directly measure how a patient feels or functions on a daily basis. Such interventions need to meet the clinical and regulatory expectations. Although QoL and functional capacity are important to patients, they currently are not typically considered as primary endpoints for HF trials for approval by the regulatory agencies. Even if they were, it remains uncertain what the stance of the payers will be if symptom improvement alone did not translate into reductions in healthcare costs.

To understand better the clinical and methodological challenges in developing endpoints that are relevant to patients beyond mortality and hospitalizations, the Food and Drug Administration (FDA) facilitated a meeting on November 12, 2015, which was attended by clinicians, researchers, regulators, and industry representatives. The focus was on expanding the paradigm for drug development in HFpEF trials, and the subsequent discussion summarizes the key takeaways from the meeting. The main goal of the meeting was to add another endpoint to mortality and hospitalization that reflect the patient journey using modern assessment techniques.

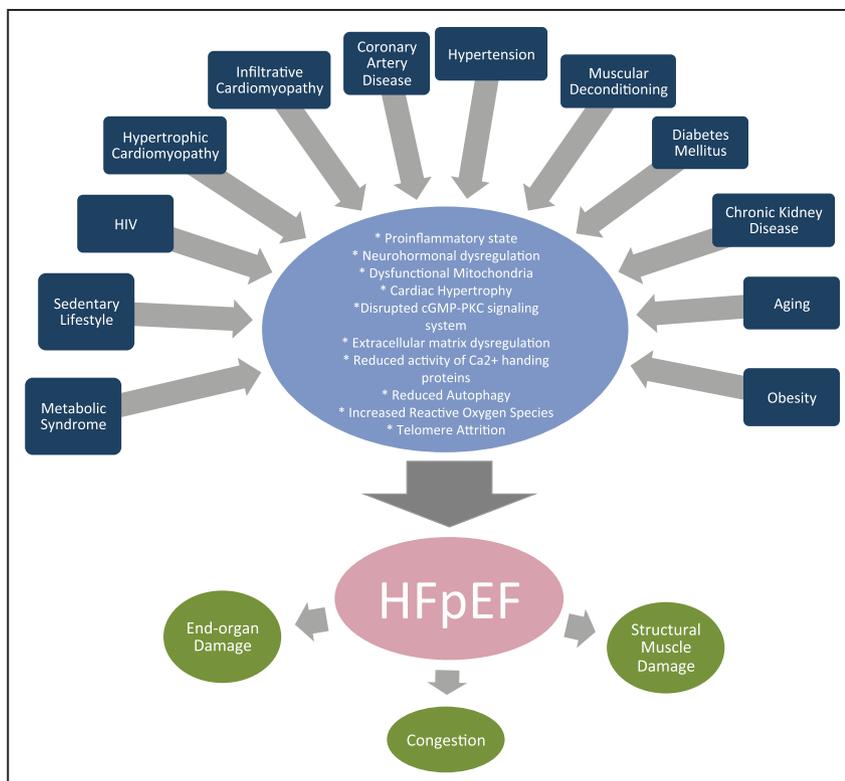
### Developing Therapeutics for HFpEF: Need for a Reappraisal

There has been substantial progress in developing drug for HF with reduced ejection fraction (HFrEF) that improves natural

history outcomes for these patients.<sup>3,4</sup> The specific approved indications are based on the endpoints of randomized trials that have involved assessments of mortality often accompanied by effects on hospitalizations, either HF related or cardiovascular. From these studies showing favorable impact of neurohormonal modulation, we can infer that an important driver of HF progression in HFrEF is neurohormonal activation. That virtually all subgroups in these trials seem to benefit in turn suggests that once the left ventricle is dilated and EF is reduced, there is a common pathway of progression irrespective of cause.

In contrast, numerous large trials in patients with HFpEF have been uniformly neutral with respect to effects on natural history outcomes. There are several potential explanations for this consistent lack of efficacy. It is possible that the natural history of patients with HFpEF is not predominantly driven by neurohormonal activation, and thus neurohormonal blocking agents are not effective. The HFpEF syndrome may comprise subgroups with distinct phenotypes and pathophysiology, with multiple prognostic trajectories (Figure 1). If outcomes are indeed driven by multiple pathways, then trying to identify 1 drug that affects natural history in a diverse group of patients using the same paradigm as for HFrEF may be futile. It would follow that attention and focus of therapeutic development should then expand its focus to also reducing symptoms and functional limitation, while assuring reasonable safety both from side effects and longer-term outcomes perspective. Patients with HFpEF may have a high burden of daily symptoms and limitations to exertion, and studies have suggested that patients with advanced HF may value improvements in these parameters more than effects on long-term outcomes.<sup>5,6</sup>

Independent of pathophysiological target, the main goal of this meeting was to include what the patients want in terms



**Figure 1.** Variable pathophysiological mechanisms for heart failure with preserved ejection fraction (HFpEF). Conditions including metabolic syndrome, HIV, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, diabetes mellitus, hypertension, aging, sedentary lifestyle, coronary artery disease, muscular deconditioning, chronic kidney disease, and obesity result in a variety of cellular changes, such as cardiac hypertrophy, increased reactive oxygen species, disrupted cyclic guanosine monophosphate-protein kinase C (cGMP-PKC) signaling system, neurohormonal dysregulation and reduced activity of Ca<sup>2+</sup> handling proteins. These processes result in the development of HFpEF with the downstream sequelae of congestion, end-organ damage, and structural muscle damage.

of signs and symptoms experienced on a daily basis as an endpoint for approval. There is precedent for a development approach focused on symptoms or functional capacity in the pathway to approval for agents. Analytic approaches that exist enable assessment of longer-term outcomes in conjunction with longitudinal measures that may reflect functional capacity. In these hierarchical approaches, if a new agent is neutral with respect to traditional outcomes but has favorable impact on symptoms or functional capacity, the new agent should win statistically. There was consensus that the concept of symptom-based or functional capacity-based development of agents for HFpEF could conceivably be undertaken, provided that safety of the treatment modality is adequately determined as well.

### Regulatory Aspects and Developmental Considerations

Regulatory agencies, including the FDA and the European Medicines Agency, recognize the importance of patient-centric endpoints, including QoL and functional capacity. For several conditions, drugs have been approved based on these outcomes. Pulmonary hypertension trials routinely assess 6-minute walk test (6MWT)<sup>7</sup> as a primary endpoint, supported by a secondary efficacy endpoint of time to clinical worsening, which is a composite endpoint that includes mortality. In such a design, a compelling 6MWT improvement combined with a time to clinical worsening composite that trends favorably, including a point estimate for the mortality component of the composite that also trends favorably and excludes a certain level of harm with a 95% confidence, has served as the basis for approval of investigational agents. Likewise, an investigational HF drug that conferred an important improvement in functional capacity, supported by a favorable trend in time to clinical worsening composite secondary endpoint, and strongly correlated with an important QoL benefit, could have a compelling case for approval in the setting of a mechanism of action that lends biological plausibility to the 6MWT improvement. Although the concept that a certain level of harm is ruled out with a 95% confidence interval is self-evident, currently there are no guidelines on what point estimate and confidence intervals will be acceptable to the regulatory and the research communities in terms of satisfying the concern that either there is no excess risk of mortality or the excess risk is within acceptable limits. It is possible that this risk tolerance actually is dependent on the magnitude of benefit. The closest example one can rely on is the experience over the past decade with drug development for diabetes mellitus, where the upper limit of 95% confidence interval was accepted when it was <1.8 during the trial and <1.3 at its completion.

However, barriers to this approach for HF drugs have included a lack of consensus around what functional capacity improvement in HF subjects is clinically meaningful and justifies some degree of uncertainty in mortality risk so long as a predefined level of harm is excluded. Another question is whether it would be acceptable to approve a drug that leads to subjective improvement in patient-reported outcomes (PRO) or objective improvement in functional capacity without any positive or negative impact on hospitalization and mortality. For a disease with high symptom burden, this is conceivable; however, further discussion is required on the exact patient

population, where this might be acceptable, and how much subjective improvement would be needed in the absence of a benefit on objective measures and hard outcomes. This trade-off would require thorough explanation to and concurrence from the patients. Indeed, the balance of benefit and risk in this circumstance will likely need to be individualized for a given agent as opposed to a one size fits all approach to all drug development scenarios.

Importantly, we have entered a new era in clinical trial design that encourages patient engagement. These new strategies encourage active patient participation from study inception, through design, execution, interpretation, and implementation. Moreover, an emerging science in PROs, the Patient-Reported Outcome Measurement Information System (PROMIS), allows for novel patient-centric outcomes to emerge as new targets for intervention.<sup>8</sup> Given the burden of HFpEF and the patient population impacted, patient engagement in study design is an inviting path to pursue.

HF is a highly prevalent high-risk disease. New medicines for HF that demonstrate important reductions in cardiovascular morbidity and mortality may be candidates for FDA programs to expedite regulatory evaluation, including Fast-Track designation, Breakthrough Therapy designation, and Priority Review. However, given the circumstance with HF of high prevalence and high occurrence rates of adverse outcomes, the FDA is not enthusiastic to conditionally approve drugs on the basis of surrogates for clinical outcomes. Experience with drugs, such as flosequinan, vesnarinone, and milrinone, that were all associated with increased mortality despite positive effects on markers of functional capacity or QoL exemplifies the potentially problematic nature of this approach.

The European Medicines Agency has an Adaptive Pathway approach to drug development to allow early patient access to medications. This approach involves 3 main principles: (1) iterative development through either approval in stages or confirming the benefit-risk of a drug following conditional approval of early data, (2) gathering evidence through real-life use to supplement clinical data, and (3) early involvement of patients and health technology assessment bodies in discussion on a drug's development.<sup>9</sup> In this case, economic considerations have an important role because if a drug is approved on the basis of a PRO, its expected price should be compared with that of drugs that may reduce mortality or morbidity. The subsequent demonstration of its ability to modify prognosis cannot lead to an increase in price.

It should be noted that when compared with a single appropriately powered trial showing convincing benefit with traditional cardiovascular outcomes that may be sufficient for drug approval, for smaller trials with alternative endpoints and higher uncertainty with respect to safety outcomes, 2 trials showing consistent results will likely be required, as is the case for pulmonary hypertension development programs. Desirable characteristics for potential alternative endpoints in HFpEF trials are shown in Table 1.

### Approaches to Study Design and Endpoints

Several endpoint designs have been proposed to avoid competition between mortality and nonmortality endpoints, to give credit to nonmortality outcomes, and to guard against

**Table 1. Characteristics of Endpoints for Heart Failure With Preserved Ejection Fraction**

Related to heart failure
Responsive to changes in disease status
Responsive to changes in patient status
Should not be a surrogate but an independent outcome
More appropriate reflection of patient-centered outcomes
Amenable to reflect longitudinal changes over time and not only a cross-sectional assessment

the safety concerns. The rank-sum procedure resulting in asymptotically normal statistics can be used for correlated endpoints to determine statistical significance.<sup>10</sup> Because it uses the average Z-score across endpoints, its application may be limited when effects are only expected in some of the endpoints or the direction of change cannot be anticipated. This approach treats each endpoint equally, however, increased weight can be assigned to certain endpoints.<sup>11</sup> The combination of multiple variables into a composite endpoint is commonly used as well. This approach is appealing because it facilitates an increase in the number of events allowing for reduced sample size, cost, and time.<sup>12</sup> However, this approach may be limited by discrepancy in the clinical relevance of the components of the endpoint, and if there are incongruent effects of the therapy on the components within the composite.<sup>13</sup> The Finkelstein–Schoenfeld method combines mortality with additional measures such that a substantial treatment difference on any of the measures will reject the null hypothesis.<sup>14</sup> The benefit to this approach is that each individual contributes to the endpoint, and thus the sample size can be smaller. Because of its hierarchical nature, there is greater emphasis on higher-order endpoints (eg, mortality or hospitalization). A global rank endpoint may be based on a multilevel outcome in a hierarchical fashion, including mortality, HF hospitalization, symptom, and functional capacity improvement, and detection of several biomarkers. A limitation of this approach is the need for agreement on the hierarchy and clinical relevance of the various components for a phase III trial.

### Mortality as an Endpoint

Improvement in mortality remains the gold standard outcome for HF trials, which is in part related to concerns about the safety of HF drugs. HFpEF patients are generally septuagenarian or octogenarian in whom the competing risk for death by other diseases is substantial.<sup>15,16</sup> Compared with patients with HFrEF, there is a lower proportion of cardiovascular death in HFpEF, ranging from 50% in observational studies to 70% in clinical trials.<sup>17</sup> Thus, even if therapies effectively targeted HFpEF pathophysiology and patient status, they may not alter all-cause mortality. In addition, in a clinical trial where patients are younger and have less prevalent and less severe comorbidity burden compared with the general patient population, the cardiovascular mortality for HFpEF patients is not as poor as for HFrEF.<sup>18,19</sup> Thus, in an older population because of the competing risk for death, and in younger ones because of a lower mortality risk within the context of a trial,

it may be difficult to improve mortality as a singular goal of therapy for HFpEF.

### Hospitalization as an Endpoint

Hospitalizations for HF are associated with poor outcomes and high costs.<sup>20</sup> There are no uniform criteria for admission or discharge for these patients. Because of financial disincentives, there is an unprecedented pressure to reduce HF hospitalizations, which may shift care to alternative venues, including frequent outpatient visits, more use of the observation units, and increased utilization of home health care and nursing homes.<sup>21,22</sup> The care provided at these alternate venues does not necessarily represent milder forms of HF because the subsequent prognosis of these patients is similar to those hospitalized.<sup>23</sup> A time to first event endpoint using admissions is problematic because it does not capture patient's overall experience, for example, a patient with a single hospitalization before a particular time because enrollment in a trial is considered worse than a patient with multiple hospitalizations if the first occurred after that time point. To account for this, some trials use a recurrent events design.<sup>24</sup> Recurrent analyses are problematic because of the competing risk of death and because subsequent hospitalizations are not independent of index admission, which need to be considered in the statistical methodology. Despite limitations, the recurrent events approach better characterizes and quantifies the patient's journey throughout the follow-up. However, frequency analyses would imply that 2 short admissions are worse than a single long complicated admission. It is for these reasons that the FDA has encouraged analysis of days alive and out of hospital. Although the days alive and out of hospital analysis may be driven by early deaths and may not, therefore, well represent the frequency or duration of hospitalizations, there may be statistical approaches applied that can normalize for time to death, such as proportion of days alive, which occurs out of the hospital. However, it is suggested that such statistical approaches are discussed and vetted with the regulators before the trial conduct to ensure that if the endpoint is reached in the trial and that it will lead to drug approval.

### Endpoints Reflecting Symptoms, Functional Capacity, and QoL

Considering the aforementioned issues, there is a need for complementary endpoints to assess other more patient-centric outcomes reflecting daily symptom burden in HF. Both functional capacity, measured objectively, and QoL scales, which are often subjective but may be captured by validated instruments, offer such opportunities.

#### Functional Capacity

Functional status can be measured by New York Heart Association classification, peak exercise oxygen consumption ( $V_{O_2}$ ), 6MWT, and potentially with wearable or implantable monitoring devices. Although the New York Heart Association class is easily assessed, it is a physician-derived measure that is subjective and amenable to bias. Peak  $V_{O_2}$  allows for direct objective measurement of maximal and submaximal exercise tolerance and is associated with both functional

ability to perform activities of daily living and outcomes. However, peak  $\text{Vo}_2$  testing is not widely available, is time consuming and costly, and is difficult to implement as an endpoint in large multicenter trials. The 6MWT is an objective measure that correlates with peak  $\text{Vo}_2$  and is easier to perform, although standardized procedures need to be followed.<sup>25</sup> The 6MWT is subject to physician bias with respect to how aggressively patients are encouraged. For this reason, if a potential drug has a side effect that functionally unblinds a trial using a 6MWT as an endpoint, the staff performing the test must not be part of the patient care team to maintain the objectivity of the test. Also, both peak  $\text{Vo}_2$  and 6MWT are not optimally performed in patients with mobility limitations. Last, the amount of improvement in 6MWT that should be considered clinically meaningful has not been well defined in HFpEF.

Implantable devices have the capability of measuring many aspects of pathophysiology, though they are used less often in HFpEF than in HFrEF patients. Such measures may give signals on how a new drug may affect physiology. Although implantable devices provide valuable information that can aid in treatment and understanding the impact of therapies, most of this information is not directly relevant to an approvable functional capacity endpoint. However, a correlation between progress in symptoms with improvement in physiology may provide impetus for accepting such improvements in alternate endpoints.

Wearable devices are evolving rapidly and may be helpful for monitoring patient activity. A recent trial used a belt with 2 kinetic activity monitors containing accelerometers.<sup>26</sup> Such devices may capture daily functional capacity in a more holistic manner. However, measured activity may not reflect the true functional capacity because activity may be limited by a lack of initiative rather than by physical limitation. One advantage of such devices is the longer monitoring period under actual life conditions. Some of these devices enable real-time reporting of safety events (eg, arrhythmias). Smart phone applications or consumer technology such as Fitbit or the Apple Watch may offer novel options as well. Because of daily variability inherent in these parameters, a preferred measurement would be the area under the curve as this may have a higher potential to detect a smaller effect compared with a change from baseline to the end of the trial only. Using such devices will require prospective studies and validation in target populations to confirm precision and accuracy of measurements. Clinically meaningful changes in device read outs need to be defined. The measurements should be precise and accurate. Generalizability of results to patients without these devices has to be considered. A correlation between endpoint improvement and reduction in healthcare cost would be important information for the payers. Furthermore, a statistically significant *P* value for a novel endpoint does not necessarily reflect a change that is of importance to the patient or their caregivers. This is particularly true in larger trials, where small, clinically insignificant changes may become statistically significant. If a novel endpoint is used in HFpEF, clinical rather than statistical significance should be ensured as a therapeutic and research goal. This, however, will require development of a consensus around the degree of change that

reflects clinically meaningful change for any intended novel endpoint. PRO assessment over the same monitoring period offers an opportunity to directly translate improved physical function into symptom improvement by the patient.

### Patient-Reported Outcomes

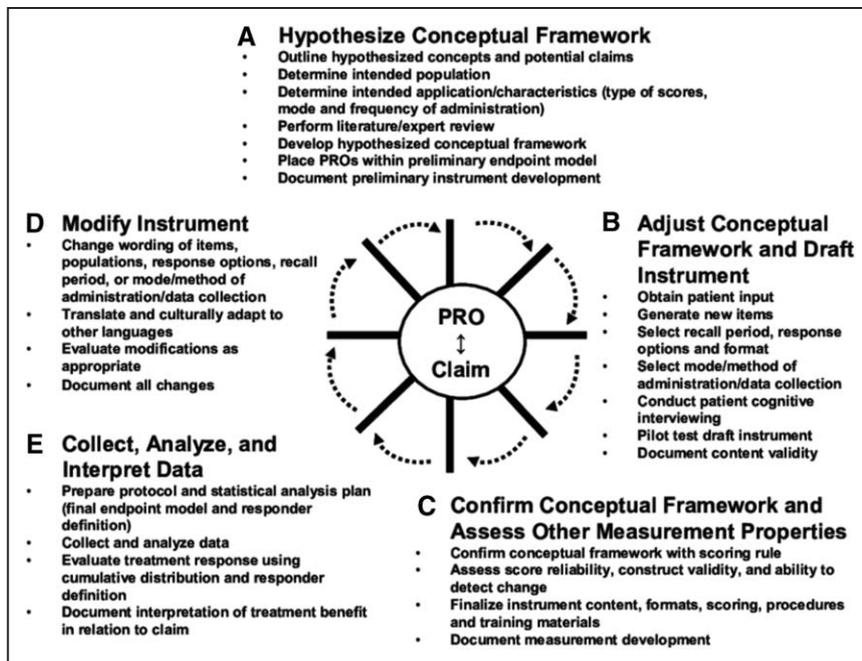
The FDA defines a PRO as any report directly from the patient about the status of their health without additional interpretation by the clinician.<sup>27</sup> A PRO can include components of functional status or QoL if deemed important by the patient. Several tools to assess QoL in HF patients have been developed (Table 2).<sup>28,29</sup> None of these completely fulfill the FDA guidelines for the development of PROs.<sup>27</sup> Also, the determinant of QoL depends on concerns larger than any given disease or drug, and aspects, such as social interference, sexual activity, and emotional wellbeing, may depend on an array of social and psychological factors beyond HF. QoL and health may be at odds in some instances, for example, defibrillators may worsen QoL<sup>30</sup> but reduce mortality in HFrEF,<sup>31</sup> whereas inotropes improve symptoms but worsen mortality.<sup>32</sup> For QoL to be an endpoint, the specific metrics should relate to the disease process and be prospectively validated for registration purposes and preferably correlate with decreased healthcare cost.

The chronicity and relentless symptom burden of HFpEF make the use of PROs critical especially because some

**Table 2. Available Instruments for Assessment of QoL**

Chronic Heart Failure Questionnaire (CHFQ)	Single-Item Health Status
Kansas City Cardiomyopathy Questionnaire (KCCQ)	Multidimensional Fatigue Inventory
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	Social Provisions Scale
Chronic Heart Failure Assessment Tool (CHAT)	EuroQoL Dimensions Index
Heart Failure Functional Status Inventory (HFFSI)	Medical Outcomes Study 36-Item Short-Form Healthy Survey
QoL in Severe Heart Failure Questionnaire (QLQ-SHF)	12-Item Short-Form Health Survey
Left Ventricular Dysfunction Questionnaire (LVD-36)	Sickness Impact Profile
San Diego Heart Failure Questionnaire (SDHFQ)	Health Utilities Index Mark-3
Memorial Symptom Assessment Scale-Heart Failure (MSAS-HF)	Patient Health Questionnaire-9
Zung Self-Rating Depression Scale	Brief Symptom Inventory
Profile of Mood State	MacNew
Patient-Generated Index	Cardiac Depression Scale
London Chest Activity of Daily Living Scale	QoL Index-Cardiac Version
Generic QoL questionnaire	Health-Related QoL Questionnaire
Cumulative Illness Rating Scale	Dyspnea Fatigue Index
Duke Activity Status Index	

QoL indicates quality of life.



**Figure 2.** Development of a patient-reported outcome (PRO): an Iterative Process. In developing a PRO instrument for clinical trials, the investigator should (A) hypothesize conceptual framework, (B) adjust conceptual framework and draft instrument, (C) confirm conceptual framework and assess other measurement properties, (D) collect, analyze, and interpret data, and (E) modify instrument. Figure obtained from Food and Drug Administration.<sup>27</sup>

patients prefer quality to length of life.<sup>5</sup> PROs allow for patient engagement a priori to determine what outcomes they consider important. According to the FDA guidelines, the development of a PRO should be an iterative process as shown in Figure 2.<sup>27</sup> Content, construct, and criterion validity, as well as the ability to detect change, should be evaluated. There are

several established psychometric properties necessary for the creation of PROs (Table 3).<sup>27,33</sup>

For a PRO to be effective, it must improve more than the day-to-day and inpatient variability of the metric. There may be a need for it to be validated in the study population in which it is used. The European Medicines Agency states that

**Table 3. Measurement Properties of PRO Instruments Used in Clinical Trials**

Measurement Property	Type	What Is Assessed?	FDA Review Consideration
Reliability	Test-retest or intrainterviewer reliability	Stability of scores over time when no change is expected in the concept of interest	-Intraclass correlation coefficient -Time period of assessment
	Internal consistency	-Extent to which items comprising a scale measure the same concept -Intercorrelation of items that contribute to a score -Internal consistency	-Cronbach's alpha for summary scores -Item-total correlations
	Interinterviewer reliability (for interviewer-administered PROs only)	Agreement among responses when the PRO is administered by 2 or more different interviewers	-Interclass correlation coefficient
Validity	Content validity	Evidence that the instrument measures the concept of interest including evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties will not replace or rectify problems with content validity.	-Derivation of all items -Qualitative interview schedule -Interview or focus group transcripts -Items derived from the transcripts -Composition of patients used to develop content -Cognitive interview transcripts to evaluate patient understanding
	Construct validity	Evidence that relationships among items, domains, and concepts conform to a priori hypotheses concerning logical relationships that should exist with measures of related concepts or scores produced in similar or diverse patient groups	-Strength of correlation testing a priori hypothesis (discriminant and convergent validity) -Degree to which the PRO instrument can distinguish among groups hypothesized a priori to be different (known groups validity)
Ability to detect change		Evidence that a PRO instrument can identify differences in scores over time in individuals or groups (similar to those in the clinical trials) who have changed with respect to the measurement concept	-Within person change over time -Effect size statistic

FDA indicates US Food and Drug Administration; and PRO, patient-reported outcome.

PROs can be used to support claims; however, for new HF drugs, PROs are generally not acceptable as the sole basis for approval because of the uncertain benefit:risk ratio.<sup>34</sup> A possible approach would be to identify the components of a PRO that the investigators think the drug of interest would target to identify suitable endpoints. Technical opportunities, such as electronically reported PROs, might avoid recall bias and offer potential benefit for future trials.

Recently, there has been increased attention to patient-centered outcomes in clinical trials, with more reports on outcomes in the domains of functional, psychological, and social status, as well as signs and symptoms.<sup>35</sup> Incorporation of the patient voice when determining meaningful endpoints is critically important to trial design. In an effort address this need, the Patient-Centered Outcomes Research Institute<sup>36</sup> was founded with the goal of funding research that focuses on questions and outcomes that matter to patients. This is accompanied by direct endorsement and engagement of patients who will be directly impacted by the study. Similarly, the FDA, through its Patient-Focused Drug Development<sup>37</sup> initiative and the Agency for Healthcare and Research Quality,<sup>38</sup> has worked toward enhanced inclusion of patient-centered goals. Thus, any further attempt to develop new endpoints for HFpEF should include patient representatives from the conception of the process.

## Conclusions

On the basis of the aforementioned discussion, the following general principles were agreed upon:

1. There is an urgent need to better understand the varied pathophysiologies of HFpEF to develop targeted therapies.
2. Patients and family concerns extend beyond mortality and hospitalization to live a life as close to normal as possible without disease symptoms.
3. Given the level of disability of patients with HFpEF, functional capacity and QoL provide endpoints relevant to the patient's journey beyond mortality and hospitalization.
4. Demonstration of substantial functional and QoL improvement could be sufficient for the registration of novel therapies, if they have an acceptable safety profile, and with noninferior mortality outcomes or exclusion of a mortality signal beyond a prespecified margin.
5. There remains a need to develop acceptable instruments for these endpoints to convince patients and providers that a new therapy is worthy of consideration.
6. What is an acceptable clinically meaningful change in PROs or activity level in HF needs to be defined. Variability in data is a concern. Changes in new endpoints may be deemed meaningful if it differs by 10% to 15% from the background variability but needs to be assessed in the context of safety. Small effects in endpoints, such as activity, can become relevant if they are in line with an appreciation of the change by the patient (eg, improved PRO).
7. The reliability, feasibility, and regulatory acceptance of an endpoint measured from a wearable monitor are uncertain, underscoring the need for prospective studies.
8. Such endpoints need to be validated to serve as the basis of approval with regulatory agencies.

9. Demonstration of cost savings associated with alternate endpoint is an important consideration to gain acceptance with payers.

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## Disclosures

Dr Butler reports receiving research support from the National Institutes of Health and European Union and serves as a consultant to Amgen, Bayer, Boehringer Ingelheim, Cardiocell, Celladon, Novartis, Trevena, Relypsa, Z Pharma, and Zensun. Dr Shah reports research support from the National Institutes of Health and the American Heart Association and has served as an advisory board member for Actelion, Bayer, Merck, and Novartis. Dr Bernstein is an employee of Merck. R. Clark and J.J. Sims are employees of Medtronic. Drs Depre, Hamer, and Maya are employees of Amgen. Dr Dinh, Dr Kramer, Kelly Lewis, S. Rotman, and Dr Roessig are employees of Bayer Pharma AG. P. Kay-Mugford and Dr Lefkowitz are employees of Novartis. Dr Patel is an employee of Merck. Dr Pitt has served as a consultant for Pfizer, Merck, Bayer, Relypsa, Stealth Peptides, AstraZeneca, Boehringer Ingelheim, scPharmaceuticals, PharMain, Tricida, DaVinci Therapeutics, Kbp Biosciences, and Takeda and has stock options in Tricida, Relypsa, Stealth Peptides, PharMain, scPharmaceuticals, Kbp Biosciences, and a patent pending, site-specific delivery of eplerenone to the myocardium. Dr Pollack is an employee of AstraZeneca. Dr Salsali is an employee of Boehringer Ingelheim. Dr Senni reports consulting fees for Novartis and Abbott Vascular. Dr Anker has received research grants from Vifor and Abbott Vascular and personal fees from Vifor, Abbott Vascular, Bayer Pharma, Novartis, Lonestar Heart, Respicardia, ZS Pharma, Relypsa, Biotronik, Cardiorientis, and Servier. Dr Zile has received research support from National Heart, Lung, and Blood Institute, Veteran Affairs, Alere, Bayer, CVRx, Medtronic, Novartis, Sanofi-Aventis and has served as a consultant for Abbott, Alere, Bayer, BG Med, Bristol Myers Squibb, Cardiome, Celledon, CorAssist, CVRx, GE Health, HDL, Idenex, Intersection Medical, Medtronic, MicroVide, Novartis, ONO Pharma, Sanofi-Aventis, and Up-To-Date. Dr Gheorghiadu reports consulting relationships with Abbott, Astellas, AstraZeneca, Bayer, Cardiorientis, CorThera, Cytokinetics, CytoPherx, DebioPharm SA, Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical, Johnson & Johnson, Medtronic, Merck, Novartis, Ono Pharmaceuticals, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, Takeda, and Trevena Therapeutics. The other authors report no conflicts.

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