HFSA Working Group

Clinical and Analytical Considerations in the Study of Health Status in Device Trials for Heart Failure

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ABSTRACT

Background: Measures of health status (including symptoms, functional status, or quality of life) assess patients' experiences of their disease, and may therefore be used to quantify the benefits and risks of treatment. The aim of this article is to provide recommendations to regulatory agencies and research sponsors regarding the use of health status measures in medical device trials.

Methods and Results: A workshop jointly planned by the Heart Failure Society of America and the US Food and Drug Administration was convened in October 2003 in Washington, DC. A Working Group to address health status measures initiated its collaboration at the workshop and continued its efforts throughout the next year. The Working Group recommended assessment of health status in all studies of heart failure therapy. Standardized instruments known to be valid, reliable, responsive to changes, and available in the languages of target populations should be used. Minimizing bias may be accomplished by using blinded, independent evaluators; collecting multiple health status measures; using valid statistical methods; and creating a health status resource bank.

Conclusion: Assessment of health status should be part of any device trial and should occur regardless of whether the device is intended as destination or bridging therapy. Health status endpoints should be chosen, collected, and analyzed with the same level of scientific rigor as traditional clinical endpoints. Regulatory agencies should require use of analytic methods that handle the complexity of health status data in addition to usual protocol protections.

Key Words: Design, endpoints, quality of life, regulatory.

The objective of this article is to make several recommendations to the US Food and Drug Administration and to research sponsors regarding the use of health status measures in medical device trials. These recommendations arose from discussions at a Heart Failure Society of America meeting during October 2003 in Washington, DC. A Health Status Working Group was formed and focused on 5 specific regulatory issues: justification for measuring health status, identification of effective measures of health status, determination of the number of health status measures, design considerations in health status device trials, and analytic considerations in using health status information. Although the information presented in this article is not meant to be comprehensive, it provides the fundamentals to support the recommendations for inclusion of health status in device trials.

What Is Health Status?

Heart failure is a disorder that includes left or right ventricular dysfunction and neurohormonal imbalances that produce physical symptoms of fatigue, edema, and dyspnea. Psychologic symptoms, such as depression and anxiety, occur frequently as well. These symptoms and other aspects

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of the syndrome of heart failure can affect an individual's physical, mental, and social function and affect the ability to perform defined tasks. Functional limitations and symptoms, in turn, can affect an individual's quality of life or physical, psychologic, and social well-being. Because the primary goal of health care is to improve and to maintain health, health status is a key outcome for the evaluation of all medical therapies, including devices. Assessments of a patient's health status thus focus on 1 or more of these components—symptoms, functional status, or quality of life. Measures of health status quantify patients' experiences of their disorder and the potential benefits and risks of treatment. We note that, although health status and quality of life have been used interchangeably, they can refer to different concepts.[1–3] In our conceptualization, health status includes the range of ways in which a disease affects a patient's life, including symptoms, function, and overall quality of life.

Many techniques and measures are used to quantify patients' health status.[4,5] Potential metrics include generic health status measures that address patients' overall health and disease-specific health status measures that quantify the specific manifestations of a given disease. The selection of the appropriate measures requires an understanding of the proposed benefits of the device, an understanding of the study population, consideration of trial design, and prespecification of the data to be collected, the potential analyses, and the desired trial interpretations. Table 1 briefly describes 2 instruments developed to specifically quantify the health status of patients with heart failure.

Why Measure Health Status in a Device Trial?

Ultimately, the primary goals of medical care are to make patients live longer and to optimize their health status. As medical options continue to expand, and now include resource-intensive device therapies, patient preference may be driven by the impact of any 1 therapy on patient's health status in all its dimensions. The first step in determining how best to quantify device effectiveness involves considering how the device might alter the health status of heart failure patients. Hence a clear conceptualization of why a particular health status instrument was chosen and the outcome it is designed to measure should be explicitly presented in the study protocol.[6] If regulatory approval is sought because the device can improve patients' quality of life, then a valid measure of quality of life should be a primary outcome measure in the trial. Likewise, sponsors might seek an indication for the device that reduces the symptoms that are important to patients with heart failure, in which case a valid measure of such symptoms should be used.

Although trials of biventricular pacing devices that are intended to improve the health and function of heart failure patients need to explicitly evaluate the health status of study patients, other devices, such as left ventricular assist devices (LVAD), may not need to include health status assessments. For example, in some trials, the time of device treatment may be short, such as use of an LVAD implanted as a bridge to transplantation. In this situation, quality of life may be a less relevant outcome to measure as compared with "survival to transplantation." On the other hand, for a device inserted as a destination therapy, quality of life may be the most important clinical outcome. For example, a patient with advanced heart failure who is not a candidate for transplantation may select an LVAD for the health status benefits it confers with respect to enhancing quality of life and reducing symptoms. It is important to note, however, that as waiting times to transplant continue to increase, the lines that delineate the intent of an LVAD insertion will "blur" and the health status effects of device therapy will become increasingly important in bridging therapy trials as well. Without health status assessments, there are no opportunities for clinicians to understand, from patients' perspectives, the impact of treatment or to apply the results of trials to better match therapies to the needs and values of individual patients. For these reasons, the Working Group recommended that measurement of health status occur in all trials, regardless of the intent to insert the device as a bridging or destination therapy.

Table 1. Examples of 2 Health Status Instruments for Heart Failure Patients

Instrument	Self-Administered	No. of Items	Domains
Kansas City Cardiomyopathy Questionnaire[9]	Yes	23	1. Physical limitation 2. Symptoms 3. Quality of life 4. Social interference 5. Self-efficacy 6. Overall summary
Minnesota Living with Heart Failure Questionnaire[21]	Yes	21	1. Quality of life

What Is an Effective Measure of Health Status?

Five key attributes of health status measures need to be present to enhance confidence in trial results.[7] Relevant psychometric properties of an instrument (Table 2) include its validity, reliability, responsiveness to change, interpretability, and availability of translations in other languages. The Working Group recommended that, in addition to a clear explanation of the outcome being measured, the study protocol explicitly address these attributes for each measure of health status for the population under study. To help establish validity, the protocol should (1) characterize relevant manifestations of the device on heart failure and (2) demonstrate that scores on the chosen measure(s) of health status discriminate patients with varying manifestations of the disorder affected by the device.[8–11] The content validity of the instrument should capture the important ways a device could affect