

## USE CASE FOR DEVELOPING NOVEL ENDPOINTS GENERATED USING DIGITAL HEALTH TECHNOLOGY: HEART FAILURE

### OVERVIEW

Despite the potential for digital technology to measure relevant data from trial participants, it is currently uncommon for endpoints generated using such technology to be incorporated into clinical trials. These endpoints could provide metrics that are meaningful to patients, but more objective and sensitive than traditional self-reported patient-reported outcomes (PROs), which are often reported alongside traditional endpoint measures.

In heart failure (HF), the traditional clinical endpoints are cardiovascular death or hospitalization with HF. Disease progression may also be followed using surrogate measures of heart function that use cardiac imaging and/or blood biomarkers. Although these endpoints may allow effective monitoring of disease progression, they do not reliably convey the burden that HF puts on patients' daily lives, nor do they gauge how patients feel. The Kansas City Cardiomyopathy Questionnaire (KCCQ)<sup>1</sup> and the Minnesota Living with Heart Failure Questionnaire (MLHFQ)<sup>2</sup> are PROs that address patients' symptoms and the effect of HF on their daily lives, but some patients describe these questionnaires as overly general and say that they do not ask questions that enable them to describe how HF is affecting their daily function. This raises a concern that existing PROs are not sufficiently sensitive. Further, these questionnaires are also limited in that they rely on self-reported retrospective and subjective assessments. Accelerometer technology, in contrast, provides opportunities to collect objective data continuously in the real world as a patient with HF goes about their daily activities.

### SPECIFIC AIMS

The aim of this use case is to describe the pathway by which a novel physical activity endpoint measured using accelerometer technology could be developed for use in conjunction with traditional clinical endpoints in regulatory submission trials in HF populations.

### STAKEHOLDERS AND INTERESTS

Stakeholders and their interests are listed below:

#### **Heart Failure Patients and Caregivers**

Heart failure patients and their caregivers are interested in the complete picture of the burden of their disease on their daily lives. They are also interested in trials that do not place excessive burdens on them (for example, in terms of number and duration of study clinic visits).

#### **Research Sponsors**

Clinical trial sponsors are interested in investigating novel indications for products, as well as making trials more efficient.

## **Clinical Investigators**

Investigators are interested in lowering burden of the clinical trial process on both their patients and their own clinical/research practices.

## **Regulators**

Regulatory agencies need to ensure novel endpoints using accelerometers represent a meaningful benefit for patients.

## **Technology Manufacturers**

Technology manufacturers (i.e., companies making accelerometers) are interested in expanding and optimizing the use of wearable accelerometers.

## **ASSUMPTIONS**

During the development of this use case, we assumed that:

1. Accelerometers generate data that are valid, reliable, and sensitive with a standardized method of data acquisition and analysis; and
2. Increasing physical activity is a desirable health benefit in patients with HF.

## **SCOPE**

During the development of this HF use case, we considered the following:

1. Developing data standards were out of scope (as this is the subject of work by another working group); and
2. Endpoints will be used in patients who have been diagnosed with HF (i.e., HF prevention is out of scope).

## **DEFINITION OF A SUCCESSFUL OUTCOME**

We consider that the development of a novel endpoint would be successful if these endpoints are able to reliably discern any meaningful change in patient's physical activity in response to a treatment such that the novel endpoint can be used to propose new indications for treatments.

## **CONCEPT OF INTEREST**

Some of the main symptoms that negatively affect the lives of patients with HF include fatigue, weakness, and shortness of breath. Potential concepts of interest discussed included measurement of strenuous activity per day (for example: measuring flights of stairs per day; number of bouts of moderate activity), measuring how long, how fast, how far, and/or how often patients walk, and measuring breathing rate or heart rate together with ambulation (for example, using the accelerometer to measure the rise and fall of the chest). It was decided that the relatively simple metric of "time spent walking" would be best for the purposes of this use case, as algorithms to derive this endpoint are in advanced development, the concept was relatively simple to understand, and it would enable the widest population of people with HF to contribute data (although it was acknowledged that time walking might increase if symptoms of HF got worse and journeys took longer as a result).

## CONTEXT OF USE CONSIDERATIONS

It was considered that successfully establishing endpoints for patients with New York Heart Association (NYHA) class I HF would be more challenging, as their capacity for physical activity may be less clearly affected by their HF. Conversely, a patient with NYHA class IV HF patient might have very little capacity for ambulation. Moreover, it is important that endpoints are able to capture both improvement and deterioration of physical capacity, which is much more easily demonstrated in the middle spectrum of heart failure severity. It was therefore decided that the focus of this use case would be on those patients with NYHA class II and class III HF (in other words, those who report mild to marked symptoms which limit ordinary activity). It was noted, however, that as the novel endpoints are perfected, the steps toward developing these endpoints could be repeated in other HF subpopulations.

## DESCRIPTION OF PROPOSED NOVEL ENDPOINT

The specific novel endpoint for this use case was therefore decided to be: *the change in daily ambulatory activity measured in minutes of walking per day using an accelerometer in patients with NYHA class II/III heart failure.*

## MAIN SUCCESS PATHWAY FOR DEVELOPMENT OF ENDPOINT

### Step 1: Analytical/Context Validation of the Novel Endpoint

This first step is to ensure accelerometers are measuring ambulatory activity. Ideally this should be confirmed in controlled environments (clinics or laboratories) but also in the real world. An example of the latter is collecting wearable camera data together with accelerometer data. From these types of data, a “validated” (reliable) algorithm for ambulatory activity in minutes per day could be derived using machine learning methods.

The best-placed stakeholders to generate these algorithms and validate them were considered to be the technology manufacturers, working in conjunction with academic investigators. Collaboration with clinicians would also allow validation to be done in the intended patient population.

### Step 2: Cross-sectional Observational Studies Correlating the Novel Endpoint with Other Measures of Heart Failure

The next step was to ensure that “time walking” correlated with measures of HF. This included ensuring that “time walking”

- ▶ Correlated with physical activity reports from general populations (this could be done with existing datasets, such as the 100,000-person UK Biobank substudy);
- ▶ Distinguished persons with and without heart failure (cases versus controls). This could also be done using the 100,000-person UK Biobank substudy,<sup>3</sup> supplemented with cases from other HF populations with accelerometer measurements (should there be an insufficient sample of people with HF in the UK Biobank); and
- ▶ Correlated with severity of HF in HF populations. This requires data from HF populations where severity of HF has been measured (by NYHA classification, established PROs, or with surrogate blood or imaging-based markers). Such data are already becoming available from the Nitrate’s Effect on Activity Trial.<sup>4</sup>

### **Step 3: Prospective Observational Studies Correlating the Novel Endpoint with Prognosis**

Prospective data assessing whether time walking predicts hard clinical outcomes (such as cardiovascular death or hospitalization with HF) would provide supportive evidence that the endpoint was measuring an important exposure, but is not essential. Additionally, analyses which assess whether “changes in time walking” observed over a period of time are associated with subsequently recorded hard clinical outcomes would provide evidence that the proposed endpoint was measuring a meaningful aspect of health.

Steps 2 and 3 would be best done by investigators and clinical trial sponsors (perhaps in collaboration) with access to relevant datasets.

### **Step 4: Assessing Whether Existing Effective Treatments for Heart Failure Improve Hard Clinical Outcomes**

Incorporating use of accelerometer technologies into current trials powered to assess hard clinical endpoints, where the novel accelerometer endpoints could be considered exploratory (and not be required to be submitted to regulators), would provide evidence that the novel endpoint is measuring a meaningful aspect of HF health. It would also provide reassurance that positive effects of a treatment on the novel endpoint were not accompanied by negative effects on hard clinical outcomes. It was discussed that this may already be possible, as such data may already have been collected serendipitously from implantable cardioversion devices in completed heart failure trials.<sup>5</sup>

### **Step 5: Establishing Consensus on How to Analyze the Novel Endpoint**

Novel endpoint analysis should follow the standard methods for trial design and analysis including blinding participants and investigators to treatment allocation wherever possible, pre-specifying analyses and considering multiplicity of testing when reporting multiple endpoints. There are several additional challenges that may need to be addressed when using the proposed novel endpoint, which include the optimum method to deal with potential biases resulting from missing data (for example: participant may die before wearing the technology; technology may fail or wear over time causing data to be incomplete in some patients). Statisticians will also be needed to help determine optimum sampling frequencies for accelerometer data collection.

### **Step 6: Future Novel Endpoints**

Development of more refined novel endpoints is anticipated over time, and Steps 1-5 would need to be completed and the novel endpoint demonstrated to at least as good, and perhaps better than the existing endpoint if the aim is to replace previous endpoints. To facilitate this work, a central database of accelerometer data from observational cohorts and trials would be a useful resource.

## **ISSUES**

There are multiple challenges that were discussed. One key topic was that HF is a complex disease that likely results from multiple underlying disease processes. For example, HF with preserved ejection fraction and HF with reduced ejection fraction have different features, so these steps may need to be repeated (or even modified) for subtypes of HF. In the case of HF with preserved ejection fraction, there is more limited randomized evidence that commonly used treatments are effective, so Step 4 will be more challenging to complete in this subpopulation.

## TO DO

Create standards for accelerometer measures and develop a central database of accelerometer data from observational cohorts and trials.

## CONCLUSION

We aimed to set out the necessary steps required to establish change in daily ambulatory activity measured in minutes of walking per day using an accelerometer in patients with NYHA class II/III HF as a novel endpoint for use in regulatory submission trials. We noted that there are several steps required which will require substantial analytical work. However, an attempt at a success outcome may soon be possible as many of the necessary tools and data for each step already exist, or are close to existing.

## REFERENCES

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- This Use Case was developed at a CTTI-hosted multi-stakeholder [expert meeting](#) in September 2016 as a part of the [DHT Novel Endpoints Project](#). Three additional Use Cases were created for trials involving:
- [Parkinson's disease](#)
  - [Diabetes](#)
  - [Duchenne's muscular dystrophy](#)