Chronic Heart Failure Working Group

Clinical Outcome Assessment Program Annual Meeting – Rockville, MD – April 9-10, 2025

Background

Rationale for Chronic Heart Failure (CHF) Working Group

- PRO Consortium member representatives and FDA advisors identified CHF as a priority area with an unmet need for a 'fit-for-purpose' clinical outcome assessment (COA) approach to evaluate clinical benefit in CHF clinical trials.
- Based on emerging technologies that enable the collection of data via mobile sensor devices (e.g., activity trackers/monitors), there is an increased interest in leveraging these for the collection of clinical trial endpoint data in patients with CHF.
- During working group formation, Amgen offered to share its developmental PRO measures and results of ongoing work exploring the use of activity monitor data in persons with CHF.

Goal of the CHF Working Group

- Develop a measurement strategy to assess symptom severity, symptom impact on physical function, and physical activity for adults with CHF by incorporating both patient-reported outcome (PRO) and activity monitor data
- Obtain FDA qualification of these measures to support efficacy endpoints in CHF clinical trials

Concepts of Interest

- Concepts of interest for the PRO measures, developed by Amgen, are self-reported severity of CHF symptoms (*Chronic Heart Failure-Symptom Scale* [*CHF-SS*]) and self-reported impact of CHF symptoms on physical functioning (*Chronic Heart Failure-Impact Scale* [*CHF-IS*]).
- Concept of interest for the step count-based measure is stepping (as an aspect of physical activity) and is reflected by specific variables related to duration of continuous steps.

Context of Use

- Target population includes adults with a clinician-confirmed history of CHF for ≥3 months with New York Heart Association class II to IV symptoms for ≥4 weeks as confirmed by medical records, documented diagnosis of CHF with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF), in stable condition for at least 4 weeks, treated with stable, optimal pharmacological therapy for a minimum of 4 weeks prior to screening.

Targeted Labeling Language

- Patients treated with [*Drug X*] reported a reduction in (or delayed worsening of) severity of CHF symptoms, if experiencing at least mild/moderate symptoms at baseline, compared with treatment [YY]. (*Based on group comparisons of means*)
- Patients treated with [*Drug X*] reported a reduction in (or delayed worsening of) limitations in physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [*Drug X*] reported an improvement in (or delayed worsening of) physical activity if experiencing limitations in physical activity at the start of the trial.

Milestones

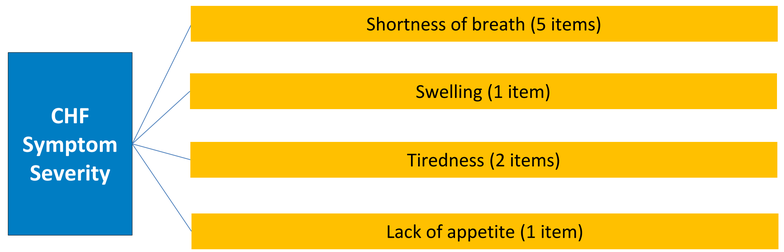
Milestone	Expected Date	Completed Date
Letter of Intent submission for 3 measures to FDA		DEC 2018
Acceptance of 3 measures into the COA Qualification Program		APR 2019
Qualification Plan submission for *CHF-SS* to FDA		MAR 2023
Qualification Plan submission for *CHF-IS* to FDA		MAR 2024
Qualification Plan submission for step count-based measure to FDA		DEC 2024
Full Qualification Package submissions to FDA	TBD	

Highlights

Example Endpoint Model for Treatment of CHF

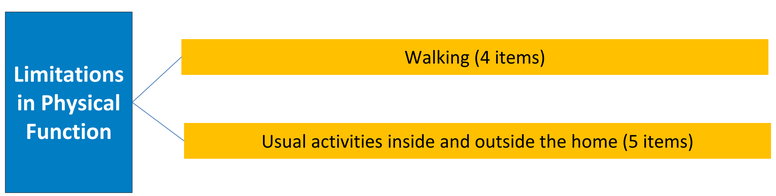
Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Time to cardiovascular (CV) death or time to heart failure event	Event rate
Secondary	Evaluate effects of [*Drug X*] on time to: • CV death • Heart failure hospitalization • All-cause death	Event rate
Potential New Primary or Secondary	Reduction in (or delayed worsening of) severity of CHF symptoms Reduction in (or delayed worsening of) limitations in physical function Improvement in (or delayed worsening of) variables related to duration of continuous steps	PRO (*CHF-SS*) PRO (*CHF-IS*) Step count-based measure (COA)

Chronic Heart Failure-Symptom Scale (*CHF-SS*) Conceptual Framework



Number of Items: 9 items addressing 4 symptom domains
Recall Period: Past 7 days
Response Options: 5 to 6-level verbal rating scale
Symptom Attribute: Intensity or frequency as a measure of severity
Data Collection Mode: Paper or tablet used for data collection (up to this point)

Chronic Heart Failure-Impact Scale (*CHF-IS*) Conceptual Framework



Number of Items: 9 items addressing 2 domains
Recall Period: Past 7 days
Response Options: 6-level verbal rating scale
Impact Attribute: Level of difficulty with performance of physical function-dependent tasks
Data Collection Mode: Paper or tablet used for data collection (up to this point)

Working Group Activities

Completed Activities

- Amgen completed a stand-alone study (N=108) to evaluate the psychometric properties of the PRO measures and the use and usefulness of an activity monitor, including evaluation of data to identify variables that could support endpoints, in January 2021; data were shared with C-Path for future analysis.
- A separate concept elicitation study (N=31) to identify the meaningful aspects of physical activity to support development of the concept of interest for the activity monitor-based endpoint measure was completed by Evidera; report submitted to FDA in July 2021.
- Advisory panel convened (December 2021; March 2022) to discuss activity monitor metric(s) that best reflect the meaningful aspects of physical activity in persons with CHF.
- Informal meeting with FDA took place in October 2022 to discuss the proposed metrics for the activity monitor-based endpoint measure and obtain FDA feedback.
- The WG determined that step count-related metrics were most appropriate to pursue, more specifically variables related to duration of continuous steps.
- Qualification Plans submitted to FDA for *CHF-SS* (March 2023), *CHF-IS* (March 2024), and step count-based measure (December 2024).
- In September 2024, DDT Research Grant awarded for *CHF-SS* to cover finalizing statistical analysis plan (SAP), conducting psychometric analyses, and preparing quantitative report.
- In December 2024, a brief *CHF-SS* Information Request was received and subsequently discussed in an informal meeting with FDA in January 2025; in February 2025, an Advice Letter was received. The working group's response was submitted in March 2025.

Unique Issues for the Working Group

- This is the PRO Consortium's first working group proposing qualification of an activity monitor-based endpoint measure.
- Main challenge has been determining what variable(s) from the activity monitor should be used to derive an endpoint.
- It remains an empirical question regarding how to incorporate the PRO data and the step count-based data to derive appropriate endpoints in clinical trials.

Work in Progress and Next Steps

- Collaboration with ActiGraph and University of Canberra, Australia, in a ground truth study to develop and validate algorithms for quantifying physical activity and step count-related metrics for adults with CHF using wearable digital health technologies; as of March 2025, data collection (n=20) is almost complete, and data analyses will begin shortly thereafter.
- Update *CHF-SS* SAP, according to feedback received in Advice Letter, and conduct analyses

Working Group Participants

Company/Organization	Representative
AstraZeneca	Folke Folkvaljon, MSc
Bayer	Luke Bamber, MSc
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Merck Sharp & Dohme, LLC	Josephine Norquist, MS
Regeneron	Katherine Kim, MPH
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