Chronic Heart Failure Working Group

12th Annual PRO Consortium Workshop – Held Virtually on April 14-15, 2021

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

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 and activity monitor data
- Obtain FDA qualification of measures to assess 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 activity monitor-based endpoint measure is physical activity with specific variable(s) to be determined.

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 reductions in severity of CHF symptoms, if experiencing at least mild/moderate symptoms at baseline, compared with treatment [YY]. (*Based on group comparisons of means*)
- Compared with [YY], significantly more patients treated with [*Drug X*] reported reductions in severity of CHF symptoms if experiencing at least mild/moderate symptoms at baseline. (*Based on group comparison using responder analysis*)
- Patients treated with [*Drug X*] reported an improvement in physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed deterioration/worsening in physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [*Drug X*] reported an improvement in physical activity if experiencing limitations in physical activity at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed deterioration/worsening in physical activity if experiencing limitations in physical activity at the start of the trial.

Milestones

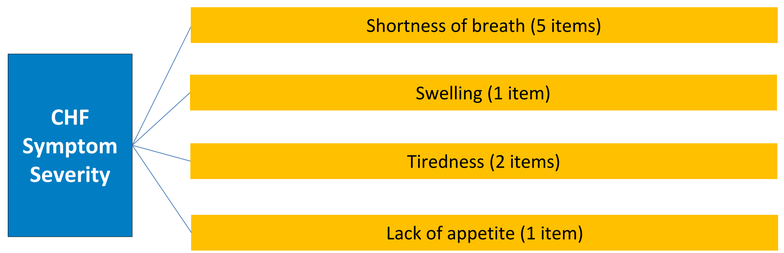
Milestone	Expected Date	Completed Date
Letter of Intent submission for three measures to FDA		DEC 2018
Acceptance of measures into the COA Qualification Program		APR 2019
Qualification Plans submission for PRO measures to FDA	TBD	
Qualification Plan submission for activity monitor-based endpoint measure to FDA	TBD	
Full Qualification Package submission to FDA	TBD	

Highlights

Example Endpoint Model for Treatment of CHF

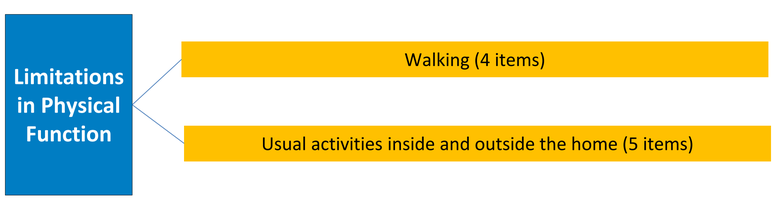
Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Time to cardiovascular (CV) death or time to heart failure (HF) event	Event rate
Secondary	Evaluate effects of [*Drug X*] on time to: • CV death • HF hospitalization • All-cause death	Event rate
Potential New Primary or Secondary	Reduction 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) activity monitor-based variable reflecting a meaningful aspect of physical activity	PRO (*CHF-SS*) PRO (*CHF-IS*) Activity monitor-based 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 agreed to share the measures with the CHF Working Group for qualification.
- Letter of Intent was submitted to FDA in December 2018.
- FDA accepted all three measures into the COA Qualification Program in April 2019.
- Cognitive interviews to obtain further qualitative evidence requested by FDA were completed by Amgen in December 2019, finalizing the content of the *CHF-SS* and *CHF-IS*.
- Data collection for 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 in December 2020.
- Amgen completed a stand-alone study (N=100) 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 will be shared with the working group for further analysis.
- Concept elicitation data analysis was completed in March 2021.
- Concept elicitation report was drafted by Evidera and is under review in April 2021.

Unique Issues for the Working Group

- This is the PRO Consortium's first working group proposing qualification of an activity monitor-based endpoint measure.
- One of the main challenges is determining what variable(s) from the activity monitor will be used to derive an endpoint.
- It remains an empirical question as to whether it makes clinical and psychometric sense to combine the PRO data with activity monitor-based data to derive a composite endpoint.

Next Steps

- Concept elicitation report will be finalized in Q2 2021.
- Qualification Plans will be submitted to FDA for the *CHF-SS*, *CHF-IS*, and activity monitor-based endpoint measure when completed.

Working Group Participants

Company/Organization	Representative
Amgen	Gary Globe, PhD, MBA; Siddique A. Abbasi, MD, MSc
AstraZeneca	Folke Folkvaljon, MSc
Bayer	Luke Bamber, MSc
Bristol Myers Squibb	Brandon Becker, PhD; Shawn Li, PhD
Eli Lilly & Company	Jiat Ling Poon, PhD; Elizabeth Nicole Bush, MHS
GlaxoSmithKline	Linda Nelsen, MHS; Robyn von Maltzahn, MSc
Janssen Global Services, LLC	Renee Pierson, MBA; Jeremiah Trudeau, PhD; John Whang, MD
Merck Sharp & Dohme Corp	Josephine Norquist, MS
Affiliation	**Other Participants**
Gwaltney Consulting	Chad Gwaltney, PhD
ePRO Consortium	Bill Byrom, PhD (Signant Health); Paul O'Donohoe, MSc (Medidata Solutions)
Université de Montréal	Marc Jolicoeur, MD, MSc, MHS
Research Partner	**Research Team**
Evidera	Milena Anatchkova, PhD; Sonal Mansukhani, PhD