Myelofibrosis Working Group

Presented at the Ninth Annual PRO Consortium Workshop – Silver Spring, MD – April 25-26, 2018

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Myelofibrosis (MF) Working Group (WG)

- Based on encouragement by the FDA to pursue qualification of a symptom measure for MF clinical trials, the PRO Consortium attempted to gain sufficient financial support from the pharma industry to begin the project. Unfortunately, the PRO Consortium was unsuccessful in this effort and the FDA was notified accordingly.
- FDA liaisons subsequently requested the PRO Consortium attempt to gain support for an initial step toward qualification. This step would involve gaining stakeholder consensus around a harmonized MF symptom assessment instrument that could be used as a provisional or interim endpoint measure until an FDA-qualified instrument became available.
- The FDA acknowledged that multiple variants of the *Myelofibrosis Symptom Assessment Form (MFSAF)* are used and believes it would be beneficial to have a single, consensus-defined instrument developed from existing empirical evidence. The instrument could be used by any sponsor with an MF drug development program. No sponsor would be required to use it, but its use would be encouraged by the FDA.

Goals of the Myelofibrosis WG

- Develop consensus around a harmonized MF symptom assessment instrument (the *MFSAF v4.0*) that can be used as a provisional or interim endpoint instrument until an FDA-qualified instrument is available.
- Assemble evidence *MFSAF v4.0* item and total scores are equivalent to variants of the *Modified MFSAF v2* that has been use in previous trials (even with minor variations in item wording).
- Assemble evidence and submit the *MFSAF v4.0 Diary* for qualification for exploratory use.

Milestones

Milestone	Expected Date	Completed Date
Identify stakeholders for Consensus Development Panel Meeting		OCT 2015
Collect all documentation to be included in review		OCT 2015
Complete review and evaluation of published and unpublished documentation of myelofibrosis symptom-targeted PRO items and instruments and provide a summary of documentation		NOV 2015
Complete final Myelofibrosis WG Information Package		FEB 2016
Convene Consensus Development Panel Meeting		MAR 2016
Complete final report in the form of a manuscript delivered to Myelofibrosis WG		MAR 2016
Conduct preliminary testing of the *MFSAF v4.0* using an internet-based survey hosted by Mayo Clinic		JUL 2017
Develop an item definition table and preliminary user manual for both recall formats of the *MFSAF v4.0*		OCT 2017
Submit Letter of Intent to FDA for exploratory use of *MFSAF v4.0 Diary*	TBD	

Highlights

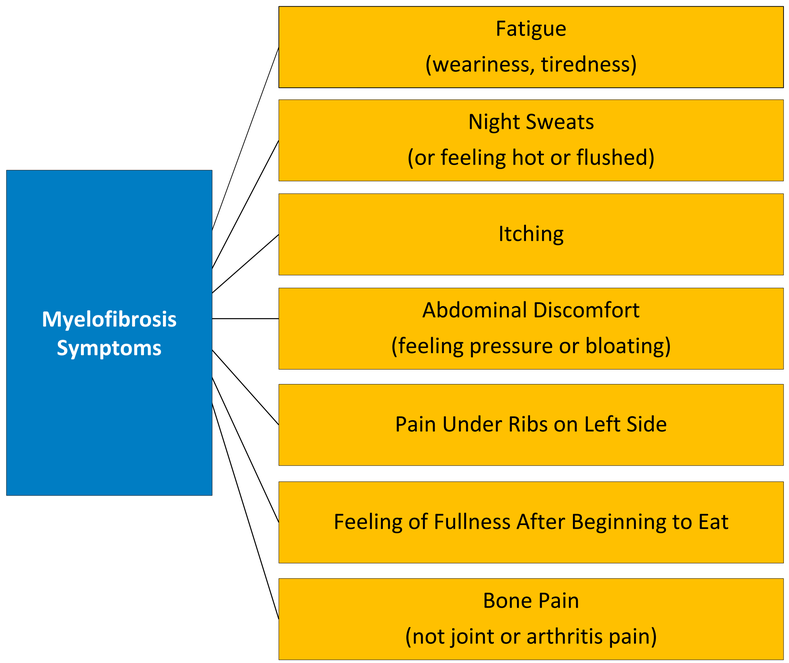
Example Endpoint Model for Treatment of Myelofibrosis

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Reduction in spleen volume	Biomarker
Secondary	Reduction in total symptom score on *MFSAF v4.0*	PRO

Target Population

- Adults aged 18 years and older with a clinical diagnosis of myelofibrosis

Hypothesized Conceptual Framework



Measure – *Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 Diary*

Consensus reached on a harmonized MF symptom assessment measure: *Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 Diary*

Core Items: Seven items covering seven individual symptoms
Recall Period: 24-hour (a 7-day format is also available)
Response Options: 11-point numeric rating scale
Symptom Attribute: Severity

Working Group Updates

Completed Activities

- Preliminary testing of the *MFSAF v4.0 Diary* was conducted in Q3 of 2017 using an internet-based cross-sectional study hosted via Mayo Clinic's REDCap Survey System:
  - Results demonstrated favorable reliability (i.e., test-retest and internal consistency), concurrent construct validity, and a high level of comparability to previous versions, both for the total score and for individual symptoms
  - The uniform use of this harmonized version in clinical trials may reduce the uncertainty of assessing symptom improvement and enable comparison across trials
  - Both recall formats of the *MFSAF v4.0* are now publicly available for use through the Critical Path Institute
- Developed item definition tables used in translating both recall formats of the *MFSAF v4.0*
- Developed user manual for both recall formats of the *MFSAF v4.0*

Information Dissemination

- Gwaltney C, et al. Development of a harmonized patient-reported outcome questionnaire to assess myelofibrosis symptoms in clinical trials. *Leukemia Research.* 2017; 59: 26-31.
- A poster was presented at the 2017 American Society of Hematology (ASH) Annual Meeting on December 9, 2017 in Atlanta, GA (manuscript forthcoming)
  - Dueck AC, et al. Quantitative Testing of the Myelofibrosis Symptom Assessment Form Version 4.0, a Harmonized Patient-Reported Outcome Measure for Collecting Key Secondary Endpoint Data in Myelofibrosis Clinical Trials
- A third manuscript investigating large-sample distributional properties of *MFSAF v4.0* data and appropriateness of using parametric statistical approaches on 11-point ordinal data will be prepared

Unique Issues for the Working Group

- Copyright/Licensing: Mayo Clinic has retained the copyright to the *MFSAF v4.0* and has granted C-Path authorization to license and distribute the *MFSAF v4.0*

Next Steps

- Quantitative Study Report will be prepared to summarize the REDCap Survey
- A Letter of Intent will be submitted to FDA proposing entry of the *MFSAF v4.0 Diary* into the COA qualification program

Working Group Participants

Organization	Representatives
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