Targeted literature review to understand the patient experience of essential thrombocythemia and to evaluate existing clinical outcome assessment measures

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Background

- Essential thrombocythemia (ET) is a rare blood neoplasm, a subtype of myeloproliferative neoplasms (MPN), characterized by clonal blood cell proliferation and excessive production of platelets[1]
- ET patients experience debilitating symptoms including night sweats, bone pain, abdominal discomfort, fatigue, fever, and weight loss, which can significantly impact their quality of life[2,3]
- ET patients are at risk for experiencing bleeding and thrombotic complications and disease progression to myelofibrosis and acute myeloid leukemia

Purpose

- As therapies are being developed for ET, it is important to have fit-for-purpose instruments to include in clinical trials to measure the ET patient experience
- While there are instruments developed for the MPN population, there are no publications capturing the ET patient experience or validation of instruments specifically in the ET population

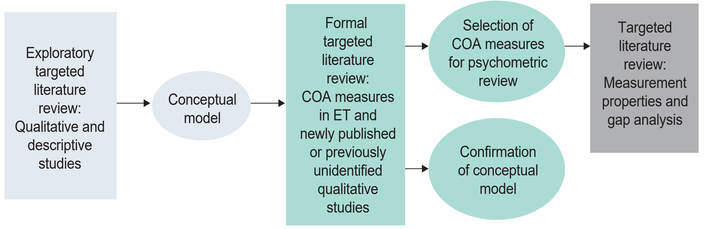
Objectives

- To conduct a targeted literature review to identify:
  - ET-specific proximal and distal symptoms and impacts to inform a patient-centric conceptual model of the ET patient experience
  - Clinical outcome assessment (COA) measures which assess each of the proximal disease-related symptoms and impacts of ET
- To map the proximal disease-defining concepts in the ET conceptual model to each of the identified COA measures
- To conduct a gap analysis summarizing the development and psychometric evaluation of identified candidate measures and the extent to which the measures have been utilized in ET clinical trials

Methods

- A review of published studies was conducted in the Ovid databases, PROQOLID™, and gray literature
- Eligible articles included:
  - ET-only populations (extended to MPN samples including ET and post-ET MF)
  - Qualitative or patient sample descriptive data
  - COA information
- Searches were limited to the past 11 years, human research, and English language
- The phased approach used to target ET literature is outlined in **Figure 1**. An exploratory search of qualitative literature in May 2023 was followed by a more formal review of COA measures and published qualitative literature conducted in October 2023

Figure 1. Phased methodology for ET targeted literature review and gap analysis

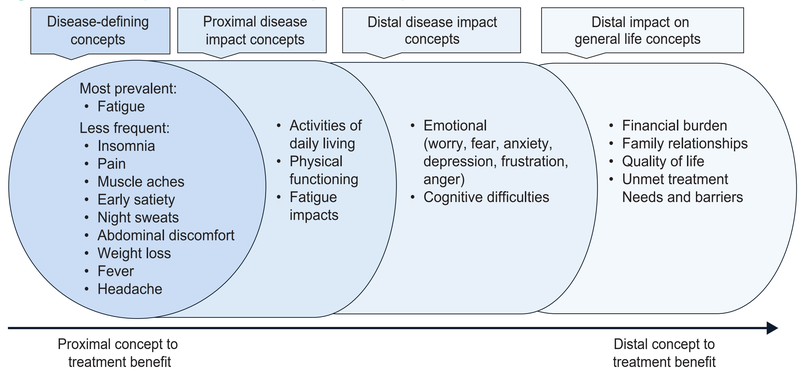


Results

Conceptual model

- An Ovid qualitative and descriptive study literature review identified 215 publications; it yielded 1 publication describing qualitative research (post-ET myelofibrosis (MF) patients)[4] and 4 observational study publications presenting ET patient data derived from 2 MPN studies, the Myelofibrosis and Essential Thrombocythemia Observational Study (MOST)[1,3] and the MPN Landmark Survey.[5] Information gleaned from these studies, together with the data from the MPN Voice of the Patient report[6] and the Patients Like Me[7] website, informed the development of a conceptual model. An additional qualitative study of MPN patients including those with ET that provided input to the conceptual model was revealed during the literature review in the second phase of the study
- The conceptual model (**Figure 2**) encompasses ET disease-defining concepts (10 symptoms, fatigue most prevalent), proximal disease impacts (physical functioning, fatigue impacts, etc), distal impacts (emotional, cognitive), and distal/general life impacts (financial, relationships, etc)

Figure 2. Conceptual model of ET patient experience



COA identification

- A targeted literature review of Ovid, PROQOLID™, and gray literature (including FDA/EMA label claims, conferences, FDA COA Compendium and NCCN guidelines) yielded 890 publications, of which 206 contained relevant data
- More than 40 COAs were identified, the majority of which were patient-reported outcome measures (PRO)
- The list of PROs were separated into 5 conceptual categories: MPN symptom-specific (n = 9), generic HRQoL measures (n = 12), fatigue-specific (n = 6), pain-specific (n = 2), psychological impact-focused (n = 8)
- Five PROs were selected for further consideration for use in ET research by examining the frequency of publication in the target population, whether it was designed specifically for ET patients, and whether it has precedence of use in clinical trials for the same/similar endpoints for ET or other MPN conditions. The five selected PROs for gap analysis were:
  - MF Symptom Assessment Form (MF-SAF) version 4.0
  - MPN Symptom Assessment Form (MPN-SAF) in its current form as the MPN-10
  - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire (EORTC QLQ-C30)
  - Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue short form 7a version (PROMIS Fatigue 7a)
  - Brief Fatigue Inventory (BFI)

Concept mapping

- Mapping of these 5 PROs with the ET conceptual model revealed:
  - MFSAF 4.0 captures 5 disease-defining concepts (fatigue, pain, early satiety, night sweats, abdominal discomfort) and no impacts
  - MPN-10 covers 7 disease-defining concepts of ET (fatigue, pain, early satiety, night sweats, abdominal discomfort, weight loss, and fever) as well as impacts of physical functioning and cognitive difficulties
  - PROMIS-Fatigue and BFI only cover fatigue and impact of fatigue concepts
  - EORTC QLQ-C30 covers some disease concepts in addition to proximal and distal disease impacts and impacts on general life (**Table 1**)

Table 1. PRO concept coverage – overview

Disease-defining concepts from the conceptual model	MFSAF v4.0	MPN-10	EORTC QLQ-C30	PROMIS Fatigue 7a	BFI
Fatigue	✓	✓	✓	✓	✓
Insomnia	X	X	✓	X	X
Pain	✓ (bone pain and pain under ribs on left side)	✓ (bone pain)	✓ (non-specific)	X	X
Muscle aches	X	X	X	X	X
Early satiety	✓	✓	X	X	X
Night sweats	✓	✓	X	X	X
Abdominal discomfort	✓	✓	✓	X	X
Weight loss	X	✓	X	X	X
Fever	X	✓	X	X	X
Headache	X	X	X	X	X
Proximal disease impact concepts					
Activities of daily living	X	X	✓	X	X
Physical functioning	X	✓ (inactivity)	✓	X	X
Fatigue impacts	X	X	✓	✓	✓
Distal disease impact concepts					
Emotional (worry, fear, anxiety, depression, frustration, anger)	X	X	✓	X	X
Cognitive difficulties	X	✓ (concentration problems)	✓	X	X
Distal impact on general life concepts					
Financial burden	X	X	✓	X	X
Family relationships	X	X	✓	X	X
Quality of life	X	X	✓	X	X

Gap analysis

- Components of psychometric validation are displayed in **Table 2** for each measure. No studies reported psychometrics specific to an ET sample, however several studies used MPN samples that included ET patients. Symbols below reflect whether validation included MPN or MF/oncology samples only
- Four of the 5 measures had published articles assessing content validity although utilization of qualitative methods with patient interviews and instrument debriefing is limited in the MPN population
- Psychometric support for each of the measures is generally strong, but specific validation in MPN or ET samples for responsiveness and meaningful change thresholds is needed

Table 2. Overview of measurement properties for reviewed measures

Measure	Content validity	Internal consistency	Test-retest reliability	Convergent or divergent validity	Known groups validity	Responsiveness	Meaningful change
MFSAF v4.0	O	✓	✓	✓	✓	☑	X
MPN-10	O	✓	✓	✓	✓	✓	X
PROMIS Fatigue 7a	⊡	☑	☑	☑	☑	O	O
EORTC-QLQ-C30	⊡	☑	☑	☑	☑	✓	X
Brief Fatigue Inventory	X	☑	⊡	☑	X	⊡	⊡

Key: ✓ = good evidence present in MPN; ☑ = good evidence present in MF only or other oncology; O = limited amount of evidence available in MPN; ⊡ = limited amount of evidence available in MF or other oncology; X = no supporting evidence identified.

Conclusions

- The targeted literature review identified fatigue as the most prevalent symptom for ET whilst physical functioning and activities of daily living were the most impactful concepts
- Although the MPN-10 has slightly more conceptual coverage than the MFSAF v4.0, there are limitations with its use in clinical studies due to the response option variations between items
- The MFSAF v4.0 content development history included MPN patients, conceptual coverage with the ET conceptual framework, and the psychometric validation included an MPN sample. Validation of the MFSAF v4.0 included confirmation that it correlates strongly with the MPN-10, MPN-SAF, and MF-SAF v2.0[8], indicating a high level of comparability to the previous versions
- The EORTC QLQ-C30 is a strong candidate PRO to use in ET populations due to its conceptual coverage with the ET patient framework as well as its strong psychometric properties and use in clinical studies. The PROMIS Fatigue 7a is a good PRO for assessing fatigue concepts in ET and is a stronger candidate for use vs the BFI, due to its fit with current guidelines for COA measures in clinical trials, including its history of use as an endpoint in clinical trials
- The MFSAF v4.0, in combination with the EORTC QLQ-C30, and PROMIS Fatigue 7a are suitable PRO measures to capture symptoms and HRQoL impacts of ET patients in a clinical trial setting
- Further research to generate further content and psychometric validity specifically in an ET population is warranted

References

1. Yacoub A, et al. *Clin Lymphoma Myeloma Leuk.* 2021;21(7):461-469.
2. Verstovsek S, et al. *Leuk Res.* 2021;110:106711.
3. Ritchie E, et al. *Leuk Lymphoma.* 2022;63(13):3138-3153.
4. Palandri F, et al. *Qual Life Res.* 2018;27(6):1545-1554.
5. Harrison CN, et al. *Ann Hematol.* 2017;96(10):1653-1665.
6. MPN Research Foundation. Voice of the Patient: A report on the first externally-led Patient Focused Drug Development meeting on Myeloproliferative Neoplasms (MPNs), November 2021. https://www.mpnresearchfoundation.org/wp-content/uploads/2021/12/2021-12-15-MPN-Voice-of-the-Report-FINAL-w-Cover.pdf. Accessed 11 May 2023.
7. Patients Like Me website. Essential Thrombocythemia: What is essential thrombocythemia?" https://www.patientslikeme.com/conditions/essential-thrombocythemia. Accessed 11 May 2023.
8. Dueck AC, Gwaltney C, Chen WH, Wang L, Pierson R, Trudeau J, Eremenco S, Coons SJ, Mesa RA. 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. Blood. 2017 Dec 8;130:2168. *Blood.* (2017) 130 (Suppl_1) : 2168. http://doi.org/10.1182/blood.V130.Suppl_1.2168.2168. https://www.sciencedirect.com/science/article/pii/S0006497119826848

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