Patient-Reported Outcome Measures in Systemic Mastocytosis: A Systematic Review

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Several SM PROMs have been developed to assess symptomology and quality of life (QoL).

The attributes, utility, and interpretability of existing SM PROMs vary widely and should be carefully considered prior to implementation in clinical trials.

INTRODUCTION

- Systemic mastocytosis (SM), driven by the *KIT* D816V mutation, leads to debilitating and unpredictable symptoms and impaired patient quality of life (QoL)[1,2]
- Assessing patient symptomology and impact of SM symptoms on QoL with valid SM-specific patient-reported outcome measures (PROMs) is critical for the evaluation of SM disease burden and treatment benefit
- The development and validation of generic and disease-specific PROMs is a multi-year process requiring several clearly established steps[3,4,5]

OBJECTIVES

- This review summarizes available SM PROMs, and profile the development, content, and application of these tools to aid in the selection of appropriate SM PROMs for use in clinical research and practice

METHODS

- We conducted a structured review of the peer-reviewed literature to identify SM-specific PROMs. PubMed, Ovid EMBASE, and clinicaltrials.gov were searched up to July 2023 to identify articles on the development and use of SM PROMs
- For each PROM, we summarize the content, development and validation history, and use in clinical trials

RESULTS

- We identified six SM PROMs: four SM symptom assessment tools and two SM QoL questionnaires. Two of the symptom assessment tools were SM subtype-specific (i.e., ISM, AdvSM); the other symptom measures and two QoL questionnaires were designed for all SM patients **(Figure 1)** [6,7,8,9]
- Each SM PROM underwent rigorous development and validation (i.e., reliability, validity, responsiveness). Robust interpretation guidelines and respondent burden varies by tool **(Table 1)** [6,7,8,9]
- The ISM-SAF is the only SM PROM that has been included in a registrational trial as a primary endpoint and is included in an approved product label.[14] It is also a primary endpoint in an ongoing trial[13]
- The AdvSM-SAF was included as an exploratory endpoint in two AdvSM clinical trials[15,14]; the MAS is an exploratory endpoint in an ongoing AdvSM trial[10]
- SM PROM content, scoring, administration, adaptations and use in clinical trials varied by measure **(Table 2)**
- The MC-QoL had fewer questions (n=27) and was used more commonly in randomized controlled trials (RCTs) than the MQLQ (n=49) **(Table 2)** [11,12,13,14]

Figure 1. Identification of SM PROMs in Scientific Literature

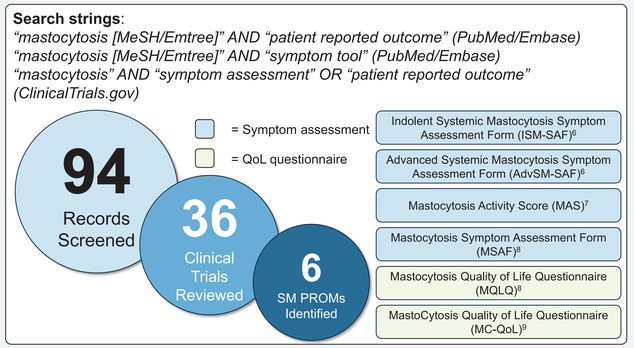

Table 1. SM PROM Development, Validation & Utility

PROM Attribute	SM Symptoms				SM Quality of Life	
	General Mastocytosis	ISM-Specific		AdvSM-Specific		
	MAS[7]	MSAF[8]	ISM-SAF[6]	AdvSM-SAF[6]	MC-QoL[9]	MQLQ[8]
Rigorous Development (e.g., conceptual framework, patient and provider input)	☑	☑	☑	☑	☑	☑
Demonstrated Reliability, Validity & Responsiveness	☑	☑	☑	☑	☑	☑
Robust Interpretation Guidelines (i.e., Severity Thresholds, Clinically Important Difference)	☑		☑		☑	
Primary endpoint in registrational study			☑[14]		☑[11,**]	
Inclusion in approved drug label			☑[19]			
Respondent Burden*	Low	Medium	Low	Low	Medium	High

*Respondent burden: low (≤20 items), medium (20-39 items, high (≥40 items); **Study ongoing for ISM indication

Table 2. SM PROM Content and Use

	Target Population	Items (#)	Symptom Domains	Individual Symptoms	Scoring	Administration/ Recall	Cultural/Language Adaptations
ISM-SAF[6]	ISM	12	Gastrointestinal, Skin, Neurocognitive	Spots, Itching, Flushing, Brain Fog, Headache, Dizziness, Nausea, Abdominal Pain, Diarrhea (frequency and severity), Bone Pain, Fatigue	**Individual symptoms**: 0 (None [symptom]) to 10 (Worst Imaginable); Diarrhea frequency **Domain scores**: 0-30 **Total Symptom Score**: 0-110	Trial: Daily with 24-hour recall Other studies: Once with 2-week recall [2, 14, 15]	Danish, Dutch,^ English,^ French,^ German,^ Italian,^ Norwegian, Polish, Spanish,^ Swedish
AdvSM-SAF[6]	AdvSM	10	Gastrointestinal and Skin	Abdominal Pain, Nausea, Spots, Itching, Flushing, Fatigue, Vomiting (frequency and severity), Diarrhea (frequency and severity)	**Individual symptoms**: 0 (None [symptom]) to 10 (Worst Imaginable) **Domain scores:** 0-30 **Total Symptom Score**: 0 - 80	Trial: Daily with 24-hour recall	Danish, Dutch,^ English,^ French,^ German, Italian, Spanish^
MAS[7]	Cutaneous Mastocytosis and ISM	9	Skin, Gastrointestinal, and Other	Itching, Skin redness/swelling, Flushing, Diarrhea, Abdominal Cramps, Muscle or Joint Pain, Fatigue, Headache, Difficulty Concentrating	**Individual symptoms**: 0 (Not at all Severe) to 4 (Very Severe) **Total Score:** Summed 7-day Total Score of 0-252, normalized to 0-100	Daily with 24-hour recall for 7 days	Arabic, Czech, Dutch,^ English,^ French,^ German,^ Greek, Hebrew, Italian,^ Norwegian, Polish, Portuguese,^ Russian, Slovenian, Spanish,^ Swedish, Turkish
MSAF[8]	ISM	22	None	Pruritus, dizziness, headache, fatigue, flushing, mediator-release attacks, dyspnoea, rhinorrhoea, palpitations, nausea and vomiting, abdominal pain, bone pain, concentration problems, and depression; Impact of fatigue on daily functioning	**Individual symptoms**: 0 (Absent/No Influence) to 10 (Very Severe/Maximum Influence) Frequency per month for "attacks" and "flushing" **Total Score**: Variable (additional "other" symptoms/impacts may be listed)	24-hour recall specific for fatigue, none specified for other questions; one-time administration	Dutch, English
MQLQ[8]	ISM	49	Fatigue and mental health, anaphylaxis, skin symptoms, bone symptoms, unfamiliarity, flushing, general symptoms, and triggers	Asks extent of being troubled by a number of symptoms	**Individual symptoms**: 0 (None/Not Applicable) to 6 (Worst Possible) **Total Score**: 0-294	No recall period specified; one-time administration	Dutch, English
MC-QoL[9]	Cutaneous Mastocytosis and ISM	27	Symptoms, Emotions, Social life/Functioning, and Skin	Diarrhea, Fatigue, Headache, Muscle/Joint Pain, Difficulty Concentrating, Sleep, Tired During the Day, Less Capable, Lacking in Motivation; Itching, Skin Redness, Flushing	**Individual symptoms**: 0 (None) to 4 (Very Much) **Total Score**: 0-108 normalized to 0-100	Once with 2-week recall	Arabic, Czech, Danish, Dutch,^ English,^ French,^ German,^ Greek, Hebrew, Hungarian, Italian,^ Norwegian, Polish, Portuguese,^ Romanian, Russian,^ Slovenian, Spanish,^ Swedish, Turkish

^Cultural language adaptations available

CONCLUSIONS

- Many SM-specific PROMs have been developed, validated, and used in clinical trials in the last several years; four quantify the severity of SM-specific symptoms and two assess patient QoL.
- The ISM-SAF has undergone rigorous validation and extensive interpretability analyses over many years, with regulatory input, to support an approved product label.
- The intended patient population, content, respondent burden, and interpretability of SM PROM data varies by tool and should be considered by clinicians and researchers to use in clinical practice, research, or quality initiatives.

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