# Development of the Mastocytosis Symptom Severity Daily Diary (MS2D2) for Non-Advanced Systemic Mastocytosis (NonAdvSM) Patients and Establishing Content Validity

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MPN-573

## INTRODUCTION

- Systemic mastocytosis (SM) is a heterogeneous disease characterized by the accumulation of neoplastic mast cells in the bone marrow and other extracutaneous tissues, with subtypes including NonAdvSM (ISM, SSM, and BMM) and advanced SM (aggressive SM, SM with associated hematological neoplasm, and mast cell leukemia).[1,2]
- The objective of this study was to develop a content valid patient reported outcome measure (PROM), the MS2D2, to assess the signs and symptoms of individuals with NonAdvSM.
  - This study builds upon a previous literature review and clinician interviews from which a preliminary disease conceptual model and draft MS2D2 were developed.
  - As part of the current study, the signs, symptoms, and impacts of NonAdvSM were further explored among individuals with NonAdvSM, the preliminary disease conceptual model was revised, and the draft MS2D2 was refined to create a final instrument reflective of the experience of this patient population.

## METHODS

### Study Methodology

**Figure 1** | Overview of Study Methodology

**Item Generation Workshop**
- An Item Generation Workshop was conducted to:
  - **Identify key concepts**: Based upon qualitative and quantitative findings, and existing instruments.
  - **Draft instrument items**: Generate an initial list of items to be tested in concept elicitation (CE) and cognitive debriefing (CD) interviews.

**Hybrid CE/CD Interviews**
- 90-minute CE/CD interviews were conducted to refine and finalize the draft MS2D2.
- Interviews assessed saturation and allowed for refinement of the MS2D2 items based on the testing of items throughout interviews.

**Concept Elicitation (CE)**
- Open-ended questions were asked to obtain spontaneous reports of signs, symptoms, and impacts.
- Patients were subsequently probed on signs, symptoms, and impacts identified from the top-line results (TLR) and clinician interviews, not spontaneously mentioned.
- Concept saturation was determined to confirm the sample size was sufficient for generalizability.

**Cognitive Debriefing (CD)**
- Patients reviewed the draft MS2D2 and provided feedback on relevance, understandability, and comprehensiveness of the instructions, items, recall period, and response options.
- MS2D2 items were added or adjusted based on patient feedback and tested in subsequent interviews.
- CD findings were summarized in an item tracking matrix.

**Item Finalization Meeting**
- A meeting with SM and PRO experts was held to integrate insights from patient interviews, clinician input, and best practices in PRO and measurement development to finalize the text of the instructions, items, and response scales of the MS2D2.

## RESULTS

### Item Generation Workshop

- The Item Generation Workshop produced an initial list of items for testing in CE and CD interviews.
  - These items assessed symptoms at their 'worst' and 'average' over a 24- hour recall period, using a 0-10 numeric rating scale (NRS).

### Interview Sample

- 18 individuals with NonAdvSM participated in qualitative interviews.

**Table 1** | Patient Demographics and Characteristics

| Baseline Characteristics | Total (N=18) |
|---|---|
| Female, n (%) | 18 (100%) |
| Age | |
| Mean (SD) | 50 (14) |
| Median | 46 |
| Range | 27-74 |
| NonAdvSM Subtype, n (%) | |
| ISM | 15 (83%) |
| SSM | 3 (17%) |
| Disease Severity, ISM, n (%) | |
| Mild | 2 (11%) |
| Moderate | 12 (67%) |
| Severe | 4 (22%) |

| Baseline Characteristics | Total (N=18) |
|---|---|
| Level of Education, n (%) | |
| High School | 2 (11) |
| Some College | 6 (33) |
| Undergraduate Degree | 6 (33) |
| Advanced Degree | 4 (22) |
| Work Status, % (range) | |
| On disability | 6 (33) |
| Unemployed | 1 (6) |
| Part-Time | 2 (11) |
| Full-time | 4 (22) |
| Retired | 5 (28) |

### Concept Elicitation | Impacts

- Patients reported 17 impacts of NonAdvSM.

**Table 2** | Patient Reported NonAdvSM Impacts

| Impact | Total number of patients reporting (N=18) |
|---|---|
| Work | 16/18 (89%) |
| Anxiety | 14/18 (78%) |
| Unfamiliarity with disease | 13/18 (72%) |
| Care management | 13/18 (72%) |
| Mood, emotions, psychological | 13/18 (72%) |
| Social interactions, personal relationships | 13/18 (72%) |
| Depression | 12/18 (67%) |
| Barriers to daily life | 12/18 (67%) |
| Mental | 12/18 (67%) |
| Appearance | 11/18 (61%) |
| Overall life satisfaction | 11/18 (61%) |
| Physical functioning | 10/18 (56%) |
| Family | 10/18 (56%) |
| Bodily function | 8/18 (44%) |
| Self-perception | 8/18 (44%) |
| Emotional state | 7/18 (39%) |
| Activities of daily living | 3/18 (17%) |

**Figure 3** | Patient Descriptions of NonAdvSM Impacts

**Work:** *"I am so careful about my work environment and... I work mostly outside or in places where I'm familiar."* – P18

**Barriers to life:** *"I can't have a hot shower or sit in a hot bath or a hot tub. Also, severe cold. I have to make sure that, if I'm going out in the snow, that I have appropriate snow pants and things on because if they're exposed to cold for too long, then they react. Certain detergents, certain chemicals they don't like."* – P16

**Social interactions, personal relationships:** *"I come here swimming and people see them [mastocytosis spots] on my chest above my swimsuit, my back. They see my thighs and it's like, 'What's wrong?'* – P05

**Appearance:** *"I wouldn't wear shorts or anything, because I was self-conscious, and he knew immediately that it was cutaneous mastocytosis."* – P17

### Concept Elicitation | Signs and Symptoms

- Patients reported 30 signs and symptoms of NonAdvSM across multiple symptom categories, with the most frequently reported being dermatology-related.

**Table 2** | Patient Reported NonAdvSM Signs and Symptoms and Corresponding Bothersome Ratings

| | Sign / Symptom* | Total number of patients reporting (N=18) | Average Bother-some rating** |
|---|---|---|---|
| Dermatology | Flushing | 18 (100%) | 4.4 |
| | Skin Redness | 18 (100%) | 3.8 |
| | Itching | 17 (94%) | 6.5 |
| | Spots | 17 (94%) | 6.0 |
| | Swelling | 14 (78%) | 6.0 |
| | Burning | 11 (61%) | 5.6 |
| Neurocognition | Brain Fog | 17 (94%) | 7.4 |
| | Difficulty Concentrating | 17 (94%) | 5.6 |
| | Dizziness | 16 (89%) | 5.3 |
| | Memory Impairment | 15 (83%) | 5.8 |
| | Headache | 15 (83%) | 5.4 |
| Gastrointestinal | Diarrhea | 17 (94%) | 4.8 |
| | Nausea | 16 (89%) | 3.5 |
| | Abdominal Cramping | 15 (83%) | 5.6 |
| | Vomiting | 7 (39%) | 6.3 |
| | Constipation | 4 (22%) | 6.5 |
| Pain | Abdominal | 14 (78%) | 7.3 |
| | Bone | 13 (72%) | 7.4 |
| | Joint | 12 (67%) | 7.7 |
| | Muscle | 4 (22%) | - |
| Fatigue | Fatigue | 17 (94%) | 8.6 |
| Other | Insomnia | 13 (72%) | 7.8 |
| | Anaphylaxis | 10 (56%) | 8.0 |
| | Allergies | 10 (56%) | 7.0 |
| | Difficulty Breathing | 8 (44%) | 7.0 |
| | Palpations | 6 (33%) | 5.6 |
| | Cough | 5 (28%) | 10.0 |
| | Osteopenia | 4 (22%) | - |

*Concepts mentioned by ≤2 patients: Difficulty swallowing (n=2), Hearing loss (n=1)
**Bothersome ratings were assessed on a 0-10 scale, where 0= not bothered and 10= extremely bothered; the average is based on participants who provided a rating.

**Figure 2** | Patient Descriptions of NonAdvSM Signs and Symptoms

**Spots:** *"It's kind of tan spots. But then as, depending on where that blotchiness is, those spots can really become prevalent and turn...sometimes almost reddish purple before the hives start."* – P11

**Flushing:** *"My face and upper body and sometimes my chest and arms just turning red and feeling kind of hot."* – P03

**Fatigue:** *"The severe exhaustion really correlates to the outbreaks, or my episodes, whatever you want to call them. Spring and fall I notice it more because I seem to react quite a bit with the warm and cold fronts."* – P11

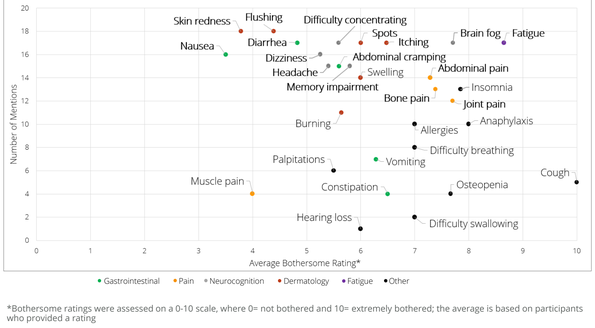
**Itching:** *"Itching is bad. Especially during attacks, my ears get all red and itchy. My palms are red and itchy. My bottom of my feet are red and itchy."* – P01

**Redness:** *"It's really bright; bright, bright red, and hot to the touch."* – P15

### Concept Elicitation | Saliency

- Saliency analysis was performed on the signs and symptoms, identifying a concept as salient if mentioned by at least 50% of patients, in combination with scientific insight.
- The analysis revealed the following 16 signs and symptoms as salient: flushing, skin redness, itching, difficulty concentrating, brain fog, fatigue, spots, diarrhea, nausea, dizziness, abdominal pain, abdominal cramping, headache, memory impairment, bone pain, and joint pain.

**Figure 4** | Saliency of Patient-Reported Signs and Symptoms Based on Prevalence and Average Bothersome Rating




*Bothersome ratings were assessed on a 0-10 scale, where 0= not bothered and 10= extremely bothered; the average is based on participants who provided a rating

### Cognitive Debriefing

- CD resulted in revisions to the MS2D2 to enhance comprehensiveness, relevance, and understandability.
- Overall, patients found the final items relevant, understandable, and easy to complete, with clear wording and response options that accurately reflected their experiences.

**Table 3** | Revisions to the MS2D2

| | |
|---|---|
| Instructions and Recall Period | The instructions and recall period were clear and well understood by all patients, with no modifications made throughout the interviews. |
| Capturing 'worst' vs 'average' symptoms | Items measuring symptom severity were globally revised to assess the 'worst' intensity of the symptom in the past 24 hours and remove 'average' intensity, due to variability, as recommended by patients. |
| Item wording revisions | Alternative item wording was tested throughout interviews, resulting in the following revisions to improve clarity:<br>• Itching: "itch" was revised to "itching".<br>• Skin Redness and Flushing: Specific body area guidance was removed.<br>• Spots: "spots" was specified to include both chronic and new spots or hives.<br>• Headache: "headache pain" was revised to "headache".<br>• Tiredness: "fatigue" was revised to "feeling of tiredness". |
| Items removed | • Anxiety, Vomiting, Insomnia, and Depression were removed as patients reported they were less directly related to NonAdvSM and better measured over a longer period.<br>• Skin Burning, Swelling, and Abdominal Cramping were removed due to conceptual overlap with pre-existing concepts and varied interpretations. |

**Figure 4** | Patient Descriptions of Cognitive Debriefing

**Worst vs average preference:** *"It's good to accommodate for fluctuations because there's a lot of fluctuations with mastocytosis. You can have really, really awful days and really, really good days, and they can be in the same day. At its worst in the past 24 is very specific to the peak of that symptom."* – P10

**Worst vs average preference:** *"Using that 'at its worst' is very helpful."* – P06

**Tiredness:** *"I think "tiredness" is better than "fatigue" because a lot of people... have no idea what fatigue is. It's not used that much in the general population, so "tiredness" is a good word I think to use."* – P10

**Itching:** *"I would almost say "itching" rather than "itch"...it makes it sound more like an active verb."* – P18

**Spots:** *"If I'm having a reaction, those everyday spots get stronger and I have the hives and the other spots. I have other spots that come up. But then as the reaction dissipates, then the everyday spots go back into being tan."* – P11

### Final MS2D2

- Using evidence from CE, four items were added to the MS2D2 based on their relevance: Brain Fog, Bone Pain, Joint Pain, and Mast Cell Reaction.
- Using evidence from CD, seven items were removed from the MS2D2 and revisions were made to enhance comprehensiveness, relevance, and understandability

**Figure 5** | Description of Final MS2D2

| | |
|---|---|
| Number of items | 17 |
| Recall period | 24 hours |
| Scales | 0-10 numeric rating scale (NRS), evaluating symptoms at their worst:<br>• Itching, Flushing, Skin Redness, Covered with spots, Nausea, Diarrhea, Abdominal pain, Bone pain, Joint pain, Difficulty concentrating, Difficulty remembering things, Dizziness, Brain fog, Headache, Feeling of tiredness |
| | Frequency (0-99):<br>• Diarrhea |
| | Occurrence (Yes/No):<br>• Mast cell reaction |

## CONCLUSION

- Concept elicitation with individuals with NonAdvSM identified 30 signs/symptoms across dermatology, neurocognition, gastrointestinal, pain, and fatigue categories.
  - 17 of these symptoms were selected for inclusion in the MS2D2 instrument.
- Interviews support the content validity of the MS2D2 in individuals with NonAdvSM.
- This study sample had a high education level and was exclusively female. As a result, there may be limitations to the conclusions drawn about the NonAdvSM patient experience.

**Presented by Carrie Nelle Lyons at the 2025 Society of Hematologic Oncology Annual Meeting**

**September 3-6, 2025 in Houston, TX**

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**Acknowledgments/Disclosures** This study was funded by Cogent Biosciences. The authors would like to acknowledge the patients who participated in the trial and those who support them, including family, caregivers, and patient advocates.