PRODUCING A NOVEL IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE SYMPTOM BURDEN SCALE (ISBUS)

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Background

Patients with idiopathic Multicentric Castleman disease (iMCD) often carry a high symptom burden, impacting many aspects of their daily life - including work/education, social life, travel, mobility, personal relationships and sexual functioning (as shown in Posters 1 and 2). The lack of curative therapies for iMCD, elevates the importance of symptom control in the clinical management of patients. Patient reported outcome measures (PROMs) are increasingly important for clinical trials and patient clinical management. The need for an iMCD specific PROM has been identified as an important gap in this therapeutic area; a position supported by the iMCD Advisory Group (December 2022 American Society of Hematology meeting, New Orleans 2022). It is expected that the creation of a novel symptom burden scale is crucial to understanding more about iMCD and may result in more timely treatment and symptom monitoring. This new research considers the prior MCD-Symptom Scale (MCD-SS) but differs in several respects. The new PROM will be developed with inputs from patients with primarily iMCD characteristics, including symptoms determined via an iterative process.

The aim of this study is to develop a PROM with strong psychometric properties that can be used to assess symptom burden in people living with iMCD in both research and clinical decision-making.

Methods

This study is an observational, non-interventionist study (NCT05995834). The study is overseen by two groups: the ASH Advisory Board that provides high level input; and the Internal Steering Committee (ISC) that advices on key elements of the protocol, such as the screening criteria, accessing patients etc. The ISC members also participate in the multi-stakeholder group (MAG).

The study follows a mixed-methods process, aggregated into four successive stages as shown in Fig. 1.

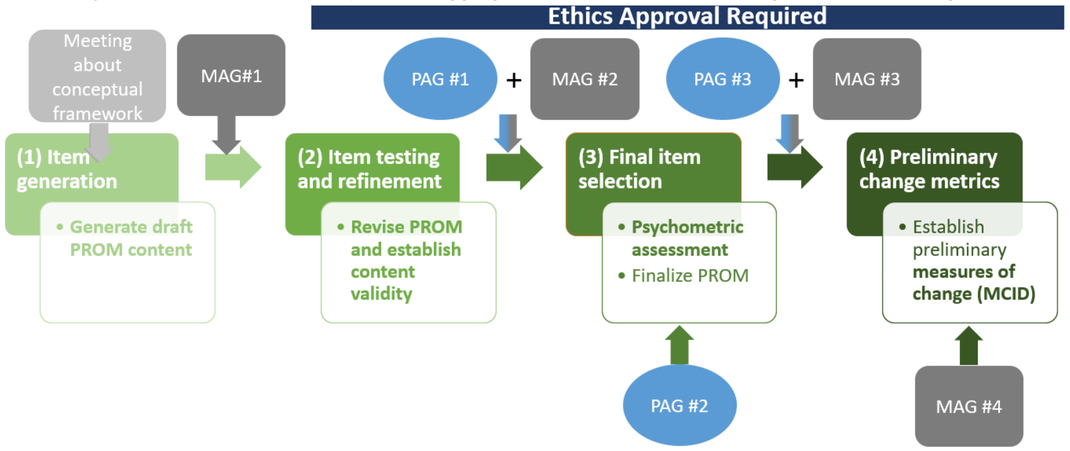

Fig. 1: Mixed-methods process for PROM development

MCID= Minimally Important Clinical Difference, MAG= Multi-Stakeholder Advisory Group, PAG= Patient Advisory Group, PROM= Patient Reported Outcome Measure

Stage 1: Item Generation

A hypothesized conceptual framework of symptom burden in iMCD was first generated from varying sources and expert opinion, including the symptom burden study.[1] Concepts included were then discussed and clarified with collaborators. Following this, draft PROM content (instructions, potential response options, potential recall periods, and candidate items) were generated by the research team. The extensive symptom list was reviewed and refined by the multi-stakeholder group (MAG).

Stage 2: Item Testing and Refinement

Ten people living with iMCD will be invited to take part in online cognitive debriefing interviews (one-on-one) to assess the content validity of the draft PROM. This assessment will consist of questions relating to the comprehensibility, relevance, and comprehensiveness, as well as the importance of different types of symptom burden on participants. The qualitative data will be analysed against existing content validity framework. The evidence will then be discussed with the MAG and the patient advisory group (PAG), and appropriate (tracked) revisions made.

Stage 3: Final Item Selection

The refined draft PROM, will be administered online as a quantitative survey, alongside sociodemographic, clinical measures of burden and/or a health-related quality of life assessment (e.g., EQ-5D-5L); N≈150 screened and consented people living with iMCD will be invited to participate. This exercise has a twofold goal: firstly, to assess statistical performance of the items, allowing for meaningful reduction of the content of the PROM. Secondly, to provide early indications of the reliability and validity of the PROM, including internal consistency, convergent and/or discriminant validity, and known-groups validity. Descriptive and psychometric analysis of the PROM will assess its performance; techniques will be tailored to suite a rare disease (small N). Further PAG and MAG consultation will follow to inform the final item selection for a concise iMCD scale.

Stage 4: Preliminary Measures of Change

To test responsiveness (sensitivity to change) and/or test reliability (consistent scores in the absence of change) the survey will be re-administered to a subgroup of patients after 2 months. iMCD being a rare disease, may be hindered by a small sample size too small to observe sufficient change, and thus reliably estimate a minimally clinical important difference (MCID). Therefore, qualitative interviews with 10 participants will also be conducted to supplement our understanding of what constitutes a meaningful difference from a patient's perspective and provide an opportunity to ask targeted questions about treatment and their impact on the patients.

Methods

Participants

Participants in Stages 2-4 are all adults that have either been physician-diagnosed or screening-assed as living with iMCD. Participants will be identified either via the Castleman's Disease Collaborative Network (CDCN) or directly via their treating physician. As this is a rare condition, convenience and availability sampling will be used. However, for the qualitative interviews, participants will be sampled from wherever possible ensuring sufficient breadth across disease characteristics, as advised by clinical experts.

Statistical Analysis

Stage 2 qualitative data will be analysed thematically against an existing framework designed to collate evidence on content validity. In Stages 3 and 4 demographics, symptom frequency and severity will be analyzed descriptively. Binary and categorical variables will be reported as frequencies and proportions within a given period. Psychometric analyses of survey data in Stage 3 and 4 will depend on the eventual sample size and may include classical test theory and Rasch analyses. At the bare minimum, quantitative information on the distribution of responses, missing responses, correlational matrices, internal consistency and reliability can be estimated. Exploratory factor analysis (EFA) will be carried out as there is some evidence that N = 50 is a reasonable absolute minimum[2] and a reasonable approach in the literature[3]. Estimates of meaningful change, including minimal clinically important difference (MCID) and responder difference (RD) will be estimated, using anchor-based and distribution-based methods. Quantitative data for Stages 3 and 4 will be collected online on Qualtrics.

Timelines

The proposed timescales are based on a start date of 7th June 2023, and are subject to timely recruitment of patients and collaborators. The study plan is presented in Fig. 2, with green indicating completed tasks.

Project tasks	Months					
	1-6	6-9	9-12	12-15	15-18	18-24
Preparatory work Kick-off meeting Protocol drafting and approval Ethics application(s) and approvals						
Stage 1: Item generation MAG workshop Confirmation of draft PROM content for Stage 2						
Stage 2: Item testing and refinement Cognitive interviews with people with iMCD Thematic analysis and qualitative synthesis Proposed revisions to PROM MAG workshop Consultation with PAG collaborators Confirmation of draft PROM content for Stage 3						
Stage 3: Final item selection Quantitative survey using draft PROM Descriptive/psychometric analyses Consultation with PAG Discussion with MAG Confirmation of final PROM content						
Stage 4: Preliminary measures of change Quantitative survey using draft PROM Descriptive/psychometric analyses Debriefing interviews with people with iMCD Thematic analysis and qualitative synthesis MAG workshop Estimate of MCID						

Fig.2: Study plan – Timescale based on 7th of June 2023 start date

MCID= Minimally Clinically Important Difference, MAG=Multi-Stakeholder Advisory Group, PAG= Patient Advisory Group, PROM= Patient Reported Outcome Measure

This study is ambitious for a rare disease, and one of the greatest limitations is patient participation to enable a large enough sample size for meaningful results.

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Poster 3

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