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Development of a core outcome set for the trials of complementary therapies in people with multiple sclerosis: international survey and consensus meetings

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ABSTRACT

Objectives This study aimed to develop a core outcome set (COS) for trials evaluating the effects of complementary therapies in people with multiple sclerosis (pwMS). We sought to identify the outcomes most relevant to pwMS, their relatives and friends, healthcare professionals and researchers and to propose these for inclusion in future trials.

Design A participatory international research project using a mixed-method approach with qualitative and quantitative methods. The study included a scoping review and a national survey in Switzerland to identify candidate outcomes, followed by an international COS survey to rate the importance of these outcomes. The final phases involved two consensus meetings to refine and finalise the COS.

Setting Data were sourced from the published literature and input from international stakeholders.

Participants pwMS and other relevant stakeholders, including their relatives and friends, healthcare professionals and researchers.

Results A total of 770 individuals participated in the international COS survey of 39 candidate outcomes (662 pwMS, 27 relatives/friends, 58 healthcare professionals and 23 researchers). According to the survey results, 13 outcomes were added to the COS, 5 were excluded and 21 were classified as 'no consensus'. 13 individuals (six pwMS, one pwMS's friend, three healthcare professionals and three researchers) attended the first consensus meeting. Following the voting on the outcomes without consensus, seven outcomes were added to the COS, four were excluded and 10 outcomes were still classified as 'no consensus'. The six members of the stakeholders advisory board (one pwMS, four healthcare professionals and two researchers) attended the second consensus meeting to define the final COS. Nine additional outcomes were included in the COS. Sexual problems, an outcome previously excluded, were also added. In total, 30 outcomes were included in the final COS.

Conclusion We have developed the first COS for future trials of complementary therapies for pwMS. The use of this COS will promote that future research in complementary therapies is relevant for pwMS and other stakeholders involved in MS care. Future COS research should integrate diverse geographical regions, where perspectives and access to complementary therapies may vary.

Study registration number https://osf.io/ys7xt/.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our core outcome set (COS) for trials of complementary therapies in people with multiple sclerosis ensured the consideration of real world needs by incorporating key stakeholders.
⇒ The survey tool randomised the order of outcome blocks, preventing participants from assigning undue importance based on position, thus enhancing the internal validity of the results.
⇒ Our multilingual COS survey enhanced inclusivity. However, we predominantly collected responses from Switzerland, which may limit the applicability of our findings to a broader international audience.
⇒ Different participants might have varying understandings of what constitutes a complementary therapy, which can affect the rating of the importance of outcomes.

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated, chronic demyelinating disease of the central nervous system, characterised by a relapsing-remitting course or progression or both. The damage caused by multifocal areas of inflammation, demyelination and axonal and neuronal loss determines burdensome

symptoms in people with MS (pwMS), such as fatigue, urinary disturbances, paresis, muscular spasms, neuropathic pain and, in time, often leads to severe disability. The two main therapeutic strategies for MS are 'disease-modifying' treatments, aimed at slowing the progression of disability and symptomatic treatments, targeting specific symptoms of MS.[1]

Complementary therapies such as yoga and acupuncture are increasingly used alongside conventional treatments for managing MS.[2] Evidence from randomised controlled trials (RCTs) suggests that complementary therapies can potentially improve numerous MS symptoms.[3 4] Complementary therapies are often perceived as providing a holistic approach to health and may empower patients by promoting active participation in their care. Some evidence suggests these therapies can improve outcomes such as stress reduction and pain management.[5]

Despite the availability of evidence from RCTs on the effects of complementary therapies, integrating these findings into MS care remains challenging. One major obstacle is the discrepancy between the outcomes measured in RCTs and those deemed relevant by stakeholders, particularly pwMS.[6 7] Furthermore, the inconsistency across clinical trials in the selection of outcomes and in the tools and time-points to measure them hampers comparing different interventions and pooling their results in systematic reviews and meta-analyses. Such limitations of research make it challenging to assess the relative effectiveness and safety of different interventions and the net benefit of each therapeutic alternative.[8 9] These challenges persist in complementary therapies for MS, where, to our knowledge, a standardised collection of relevant outcomes is still lacking.

A core outcome set (COS) is an agreed standardised list of outcomes that should be measured and reported, as a minimum, in all clinical trials of a specific clinical area.[10] A COS should be derived from consensus among individuals affected by the condition and other relevant stakeholders, including patient representatives, healthcare professionals and researchers. There is a growing global initiative to advocate for the development and utilisation of COS. This movement is led by organisations such as the WHO, Cochrane, trial registries, journal editors, research funders and regulators, such as the European Medicines Agency.[11–14]

Developing a COS for trials evaluating complementary therapies in pwMS is essential for numerous reasons related to mitigating research waste.[15] First, incorporating a COS in trials ensures that outcomes relevant to patients, healthcare professionals and other stakeholders are prioritised. Prioritising outcomes can help streamline the focus of future research, ensuring that the most relevant outcomes are measured, while allowing flexibility in assessing other outcomes based on the specific context of each trial. This approach will generate relevant evidence for informed decision-making.[16] Second, adopting a shared COS in future trials of complementary therapies for pwMS will promote consistency in outcome evaluation, enhancing the precision of treatment effect estimates in meta-analyses.[17] It is important to design large clinical trials of complementary therapies that are adequately powered to detect small effects. While some complementary therapies may provide modest benefits, their greater acceptability and safety for pwMS compared with drugs with similar effect magnitudes may result in a higher net benefit. Therefore, enhancing methodological consistency in research on complementary therapies for MS is crucial to improve the precision of treatment effect estimates.

Survey and consensus methods were selected for this project to capture the diverse outcomes relevant to different stakeholders in MS. This approach enables the integration of expert perspectives, ensuring the development of a widely applicable COS. Existing COSs for MS focus primarily on outcomes related to pharmacological treatments, falls or exercise.[18–21] However, a COS tailored specifically to complementary therapies is needed, as these therapies address broader aspects like quality of life and mental well-being, which are often overlooked. A dedicated COS would better align research with the holistic nature of complementary therapies for pwMS.

This study aims to develop a COS for trials on complementary therapies in pwMS. This COS will contain the most relevant outcomes for relevant stakeholders globally, particularly pwMS.

METHODS

This study was a five-phase participatory research project using a mixed-methods approach that combined qualitative methods (content analysis), quantitative methods (descriptive analyses) and consensus procedures (figure 1). The study began with a scoping review and a national survey in Switzerland to identify candidate outcomes, followed by an international COS survey involving pwMS and professionals to rate the importance of these outcomes. The final phases involved two consensus meetings to refine and finalise the COS. This participatory mixed-methods approach ensured both indepth understanding and broad stakeholder input—critical elements when defining outcomes for complex interventions such as complementary therapies.

We followed the Core Outcome Measures in Effectiveness Trials (COMET) handbook and the COS-Standards for Development[15 22] to develop the COS. This manuscript meets the COS-STAndards for Reporting guidelines[23] and the ACcurate COnsensus Reporting Document guidelines for consensus methods in biomedicine.[24] The COS protocol was prospectively registered on Open Science Framework (OSF), 19 April 2024 (https://osf.io/ys7xt/). See online supplemental file 1. There were no changes from the protocol.

Patient and public involvement

Patients and the public were involved in the design, conduct, reporting and dissemination plans of our

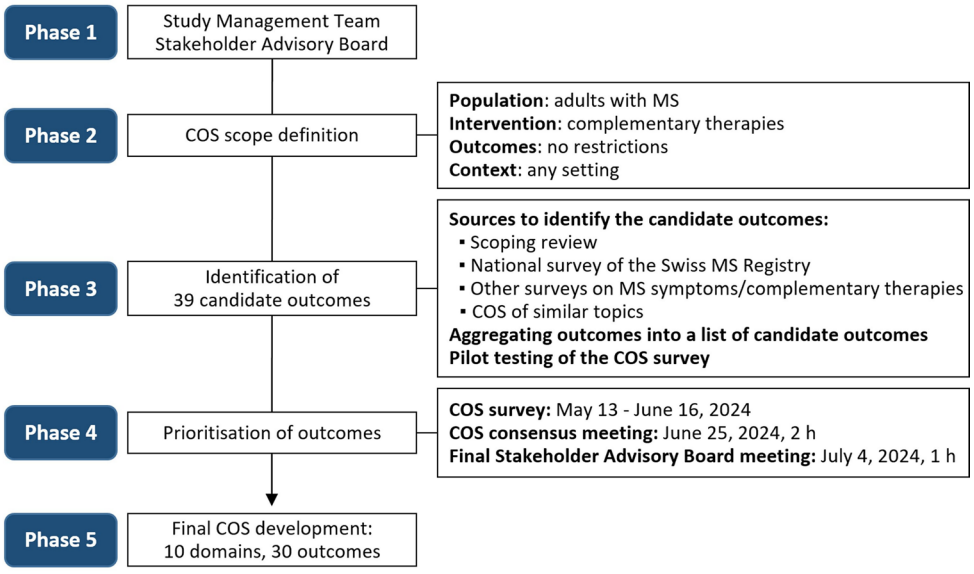

Figure 1 COS development phases. COS, core outcome set; MS, multiple sclerosis

research. The involvement of the key stakeholders, that is, pwMS, relatives and friends, healthcare professionals and researchers, was integral to this project from inception. First, the results of a national survey of pwMS in Switzerland informed the list of candidate outcomes for the COS survey (pending publication). Second, the draft COS survey was sent to the Swiss MS Society[25] and the Swiss MS Registry[26] to incorporate the feedback from pwMS. Third, pwMS, healthcare professionals and researchers contributed to the final COS by disseminating and completing the COS survey and participating in the consensus meetings. Additionally, the project's stakeholder advisory board was comprised of healthcare professionals, researchers and one pwMS, all of whom are co-authors of this study. The stakeholder advisory board will also be involved in the dissemination plans of the study results, assisting in deciding what information to share, when and in what format. The stakeholder advisory board was not reimbursed for its time, demonstrating their commitment and the collaborative nature of this research.

Phase 1: Study management team and the stakeholder advisory board appointment

The study management team consisted of six members (AKT, CC, CMW, JB, JLA and YY), all based at the Institute for Complementary and Integrative Medicine and Cochrane Satellite Complementary Medicine (University Hospital Zurich). The study management team coordinated and delivered the entire project, bringing expertise in complementary therapies (CC, CMW and YY), trials (CMW and JB), systematic reviews (AKT, CMW, JB, JLA and YY), as well as qualitative research and stakeholder engagement (CC and CMW).

The stakeholder advisory board was created using a purposive sampling strategy to include key stakeholders.[27] It was a multidisciplinary group of six members, predominantly women (4/6; 66.7%), all living in Switzerland, comprising one pwMS (GR), three healthcare professionals with experience in MS (two neurologists, SHL and CB, and one nurse, SB) and two researchers (epidemiologists from the Swiss MS Registry, VvW and NS). Two healthcare professionals had extensive experience with complementary therapies. The stakeholder advisory board contributed to the COS development by overseeing the COS study, providing feedback on the study protocol and the list of candidate outcomes, contributing to the development and dissemination of the COS survey, codeciding the final COS and disseminating the COS.

Phase 2: COS scope definition

This COS for trials on complementary therapies in pwMS contains the most relevant outcomes for stakeholders. The COS proposes 'what' outcomes to consider but does not recommend 'how' or 'when' to measure these outcomes.

Population and health condition: adults with MS

Our COS targeted the needs and characteristics of adults (18 years or older) diagnosed with MS, irrespective of their demographic or MS characteristics, such as age, sex or MS type and disease severity.

Intervention: complementary therapies

Complementary therapies are therapies typically outside the scope of conventional Western medicine and are used alongside conventional treatment.[4] This COS applies to manual therapies (eg, acupuncture, massage or reflexology), mind-body therapies (eg, meditation, yoga, tai chi), natural products-based therapies (eg, cannabis, herbs, vitamin and mineral supplements or aromatherapy) and specific diets (eg, gluten-free diet). Online supplemental file 2 details the eligible and non-eligible interventions, compiled from relevant sources[28–30] and through engagement with stakeholder groups and the

stakeholder advisory board. We acknowledge that some of these interventions—such as massage, vitamin/mineral supplements and dietary changes—may be used in both complementary and conventional settings. Still, these 'grey zone' interventions can be considered complementary if they are not used as part of routine MS care.

Outcomes and context

Our COS aimed to include the most relevant outcomes for all stakeholders interested in MS, including pwMS and their relatives and friends, healthcare professionals with experience in MS and researchers. These outcomes may not be exclusive to MS. Therefore, our COS admitted outcomes that might also be relevant to other health problems, given the shared nature of specific symptoms or therapeutic goals across different conditions.

Phase 3: Candidate outcomes identification

In phase 3, we generated a list of candidate outcomes relating to complementary therapies in pwMS.

Sources to identify the candidate outcomes

We performed a scoping review following Joanna Briggs Institute methods[31 32] to inform the COS. This scoping review identified complementary therapies and outcomes assessed in systematic reviews and RCTs including pwMS. The review protocol was registered on OSF (19 May 2023): https://osf.io/axwu2, online supplemental file 3). The results of the scoping review will be published elsewhere. From October 2022 to August 2023, the Swiss MS Registry conducted a national survey on 888 pwMS in Switzerland to identify, among other characteristics, the symptoms for which they use complementary therapies. The results will be described elsewhere (manuscript submitted). In addition, we identified other surveys on symptoms or complementary therapies used among pwMS.[3 33–36] We also considered available COS in other clinical areas, such as Parkinson's disease, post-COVID conditions or pharmacological interventions for MS.[18 19 21 37] These COSs were reviewed to identify outcomes relevant across neurological conditions and to ensure that commonly used outcome domains—such as fatigue, cognitive function and quality of life—were not overlooked. Additionally, they provided structural guidance for grouping and labelling outcomes in our survey, ensuring alignment with prior work.

Aggregating outcomes into a list of candidate outcomes

All outcomes identified in our searches were extracted in a Microsoft Excel form according to the COMET taxonomy of core domains, which has five areas: death, physiological/clinical, life impact, resource use and adverse events.[38] We generated a shorter list of candidate outcomes to be rated in the survey. Duplicated outcomes were eliminated, and the outcomes were grouped in domains following a similar structure as a recently published COS for MS (the Standard Outcome Set for Multiple Sclerosis: S.O.S. MS project),[18] this one not focusing on complementary therapies. The full process and criteria applied to group the outcomes will be described in the scoping review article.

COS survey pilot testing

The candidate outcomes were incorporated into the online SoSci survey tool.[39] The survey was available in English, German, French, Spanish and Italian. Translations into German, French and Italian were conducted from English by the professional translation team of the Swiss MS Registry (University of Zurich), which regularly translates surveys for the national MS cohort in Switzerland. These translations followed established procedures to ensure conceptual and cultural equivalence. The Spanish translation was conducted from English by JL-A, a trained medical doctor, study author and native Spanish speaker who has been involved in the project since its inception. Although a full back-translation process was not applied, each translated version was piloted by at least one native speaker to ensure clarity and relevance. The study management team reviewed all language versions for consistency. The piloting team included experts in complementary and integrative medicine, such as the study authors CMW and CC, ensuring that translations remained faithful to the intent and context of each outcome. Outcomes were further refined during piloting by combining, condensing or removing unclear or redundant items.

Phase 4: Outcomes prioritisation

The candidate outcomes were discussed through an international, multi-stakeholder consensus process involving an international survey and two consensus meetings (one first meeting with selected participants and a second meeting with the stakeholder advisory board to generate the final COS).

COS survey

Survey participants

We aimed to reach adults representing diverse stakeholders interested in MS or complementary therapies: pwMS, their relatives and friends, healthcare professionals and researchers. The experience in receiving or delivering complementary therapies was not an inclusion criterion for participation. We widely distributed the survey link to stakeholders at both national and international levels. The survey was announced through newsletters, websites and social media (Facebook, LinkedIn, Instagram, X) of organisations such as the Swiss MS Society, Swiss MS Registry, Institute for Complementary and Integrative Medicine homepage, LinkedIn channel of the Epidemiology, Biostatistics and Prevention Institute at University of Zurich, European MS platform, European Federation of Pharmaceutical Industries and Associations, Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System, Cochrane Complementary Medicine, University Hospital Zurich Health Professionals newsletter and Deutsches Ärzteblatt (German Medical Association's official science journal). Further, we sent personal invitations via email to individuals in our network and to authors of complementary therapies studies included in our scoping review. Participants were asked to pass on

study details to their contacts. No incentives were offered to participate in the survey.

COS survey format, data collection and confidentiality

The multilingual, anonymous, open and voluntary online survey was delivered through SoSci Survey[39] (online supplemental file 4). In the first section, the participants' characteristics were collected. pwMS were also asked about their previous use of complementary therapies. Healthcare professionals reported their main profession, experience in managing or treating pwMS and experience providing complementary therapies.

Participants scored the importance of 39 candidate outcomes on a three-point Likert scale from one to three (one indicated that the outcome was 'not important', two indicated 'important' and three indicated 'very important'). Participants could also select 'unable to respond'. Through free-text entry, participants could provide comments or suggest additional outcomes. The outcomes were presented in groups in random order for each participant. Finally, participants could indicate if they wanted to participate in the online consensus meeting. If this was the case, they were redirected to another online form to collect their contact details.

The survey responses were anonymous. Participants' consent was sought online prior to accessing the survey. All data were handled confidentially and in accordance with local data protection regulations under Swissethics. The survey data were anonymously stored on the SoSci Survey platform hosted on a server of the University Hospital Zurich. In the final survey section, respondents were invited to join an optional online consensus workshop, with responses stored separately. Participants provided personal details, and all data were securely collected at University Hospital Zurich, following strict privacy policies. No compensation was given, but workshop attendees were offered coauthorship of the manuscript if they met criteria.

Consensus criteria

We considered the consensus criteria for each outcome as predefined in the COS protocol[40] (table 1). For the consensus, we considered four stakeholders' groups: (1) pwMS or relatives/friends; (2) healthcare professionals with at least some experience in providing complementary therapies; (3) healthcare professionals without experience in providing complementary therapies and (4) researchers.

Data analysis

Statistical analyses were performed with R software.[41] The analysis included all respondents who provided consent, identified their stakeholder group and rated at least one outcome. We described the participants' characteristics by using percentages for categorical variables and means and SD or medians and IQR for numerical variables. For each outcome, the total numbers and percentages of participants rating the outcome as 'not important', 'important', 'very important' or 'unable to respond' were presented. Rating results for each outcome were stratified by stakeholder group. Qualitative thematic analysis was conducted to group participants' comments into overarching categories,[42] identifying any uncaptured outcome. The study management team reviewed additional proposed outcomes and, if applicable, carried them forward to the final stakeholder advisory board meeting.

COS consensus meeting

The online consensus meeting aimed to reach an agreement on the outcomes that did not achieve consensus during the survey. The consensus method involved a meeting where participants discussed and voted to reach

Table 1 Consensus criteria

Decision	COS survey	COS consensus meeting	Final stakeholder advisory board meeting
Consensus in	The following criteria are met in group 1 and, at least, in one of the other groups (2, 3 or 4) *: ≥70% scoring as 'very important' † and <15% scoring as 'not important' † and <30% of the sample scoring 'unable to respond' ‡	≥70% of the meeting participants voted that the outcome is 'Very important'	The stakeholder advisory board agreed to include the outcome in the COS
Consensus out	The following criteria are met in Group 1 and, at least, in one of the other groups (2, 3 or 4) *: <50% scoring as 'very important' † and <30% scoring 'Unable to respond' ‡	<50% of meeting participants voted that the outcome is 'Very important'	The stakeholder advisory board agreed not to include the outcome in the COS
No consensus	Anything else	Anything else	–

*Group (1) pwMS or relatives/friends; (2) healthcare professionals with, at least, some experience in providing complementary therapies; (3) healthcare professionals without experience in providing complementary therapies and (4) researchers.
†Denominator: total number of participants scoring the outcome (1, 2 or 3). Participants providing no score or 'Unable to respond' were not considered in the denominator.
‡Denominator: total number of participants answering this outcome (with a score or 'Unable to respond').
COS, core outcome set.

an agreement. The interactions during the meeting were non-anonymised, but the process included anonymous structured voting.[24] The meeting, conducted in English, was chaired by JB from the study management team, who tried to ensure equal opportunity for all participants to share their views before voting. The study management team attempted to recruit a representative group of 9–20 individuals, aiming for 50% pwMS, to ensure a manageable group size that allowed for meaningful discussion while maintaining diverse stakeholder representation. Including at least half of the pwMS ensured that their perspectives—central to the COS—were prioritised in the consensus process. Participants were invited, on completing the survey, to provide contact details if interested in participating in the consensus meeting. Moreover, interested individuals from the network who did not respond to the survey were also eligible. Participants were not reimbursed for their time but were invited to be coauthors of the article.

The meeting was conducted online and video-recorded, after participants consented, using a password-protected Zoom platform. It lasted 2 hours, including a 5-minute break (see online supplemental file 5 for consensus meeting materials).

The focus was on the outcomes without consensus in the survey. Initially, there was an open discussion on the outcomes without consensus, followed by voting on the inclusion/exclusion of the outcomes without consensus. Survey results were presented for each stakeholder group (1–4), showing whether the stakeholder group considered this outcome to be included in the COS.

Participants voted anonymously via mentimeter[43] on the inclusion of each outcome in the COS, choosing 'yes,' 'no' or 'I prefer not to respond.' Responses were directly displayed as percentages during the meeting. Consensus rules followed the approach detailed in table 1. A guided discussion followed to address the outcomes for which consensus had not been reached during the voting.

Final stakeholder advisory board meeting to agree on the final COS

The final meeting with the stakeholder advisory board aimed to confirm the excluded outcomes and make a final decision on the outcomes on which consensus had not been reached in the previous phases. CMW, project lead and member of the study management team, chaired the meeting and worked to ensure that all participants had an equal opportunity to share their views.

The meeting included discussions, was conducted in English and aimed to reach full agreement within the stakeholder advisory board. It was conducted online via a password-protected Zoom platform and lasted 1 hour (see online supplemental file 6 for the meeting materials). First, attendees were asked to confirm their agreement on the decision for the outcomes excluded in previous project phases. Second, they discussed the inclusion/exclusion of outcomes without consensus from the previous meeting. Ratings for each outcome from the survey and first consensus meeting were presented for each stakeholder group (1–4). Attendees were shown the percentages of survey respondents and meeting participants who rated each outcome as 'very important'. Group differences were highlighted and discussed.

Phase 5: Final COS development

The manuscript draft containing the final COS was emailed to the consensus meeting participants who wished to be coauthors, as well as to the stakeholder advisory board. Their feedback was incorporated, and the final version of the COS was approved.

RESULTS

Phase 3: Candidate outcomes identification

The results of the scoping review and the national survey of the Swiss MS Registry to identify the outcomes will be described in separate manuscripts. The study management team and the stakeholder advisory board agreed on a list of 39 outcomes to be included in the COS survey.

Phase 4: Outcomes prioritisation

Online survey

The survey was conducted between May 13 and June 16, 2024. During this period, 1900 users clicked the survey link, but 991 left the survey on the introduction page. Out of the 909 who continued, 903 consented to participate, of which 770 (85.3%) participated in the survey. 602 out of 770 participants (78.2%) answered all outcomes. Table 2 details the characteristics of the survey and COS consensus meeting participants.

According to our consensus criteria, 13 out of the 39 outcomes (33%) met the criteria for 'consensus in', five outcomes (13%) met the criteria for 'consensus out' and 21 (46%) outcomes were still classified as 'no consensus' (see table 3 and online supplemental file 7).

The survey respondents identified nine outcomes via free text comments, but the study management team decided that they would not be discussed by the stakeholder advisory board for inclusion. Four of these outcomes were already covered in the list of candidate outcomes ('fears about the future' was covered by anxiety, 'taking care of your family' by the ability to work/perform daily activities, 'food security' and 'heavy metal pollution' were covered by the safety of complementary therapies). Additionally, 'Price of complementary therapies' was proposed, but the study management team excluded this outcome as it is not considered as an outcome of efficacy/safety but rather a factor related to feasibility/acceptability of complementary treatments. Besides, cost and reimbursement may vary in different healthcare systems. The study management team determined that two proposed outcomes were not of the highest importance for inclusion in the COS ('health literacy' and 'malnutrition'). The study management team considered that 'female cycle, that is, menstruation, menopause' was not a health problem or symptom. Finally, the study management team decided to include 'prostate problems' under

Table 2 COS survey and COS consensus meeting participants

	COS survey					COS consensus meeting
	Total sample	People with MS	Relatives/ friends	Healthcare professionals	Researchers	
	n=770*	662 (86.0%)	27 (3.5%)	58 (7.5%)	23 (3.0%)	n=13 †
Gender, n/N (%)						
Woman	580 (75.3)	512 (77.3)	21 (77.8)	40 (69.0)	7 (30.4)	7 (53.8)
Man	181 (23.5)	147 (22.2)	6 (22.2)	14 (24.1)	14 (60.9)	6 (46.2)
Other	7 (0.9)	2 (0.3)	–	4 (6.9)	1 (4.3)	–
I prefer not to answer	2 (0.3)	1 (0.2)	–	–	1 (4.3)	.
Age in years						
Mean (SD), N	50.6 (12.7), 769	50.3 (12.2), 662	46.4 (14.0), 27	48.9 (14.3), 58	40.4 (15.6), 23	50 (15.8), 12
Median (Q1, Q3)	51 (41, 60)	51 (41, 59)	51 (33.3, 55)	48 (36.3, 58)	36 (26.5, 54.5)	47 (39.3, 62)
Country of residence, n/N (%)						
Switzerland	671/760 (88.3)	615/654 (94.0)	20/25 (80.0)	34/58 (58.6)	2/23 (8.7)	8/13 (61.6)
Germany	18/760 (2.4)	16/654 (2.4)	–	2/58 (3.4)	–	–
Spain	16/760 (2.1)	1/654 (0.2)	1/25 (4.0)	10/58 (17.2)	4/23 (17.4)	–
USA	10/760 (1.3)	1/654 (0.2)	–	4/58 (6.9)	5/23 (21.7)	1/13 (7.7)
Italy	7/760 (0.9)	4/654 (0.6)	–	1/58 (1.7)	2/23 (8.7)	2/13 (15.3)
France	7/760 (0.9)	5/654 (0.8)	1/25 (4.0)	1/58 (1.7)	–	–
Iran	6/760 (0.8)	1/654 (0.2)	2/25 (8.0)	2/58 (1.7)	1/23 (4.3)	1/13 (7.7)
Mexico	1/760 (0.1)	1/654 (0.2)	–	–	–	1/13 (7.7)
Other countries	24/760 (3.2) ‡	10/654 (1.5) §	1/25 (4.0) ¶	4/58 (6.9) **	9/23 (39.1) ††	–
Complementary therapies use by pwMS, n/N (%)						
Previous use	NA	516/651 (79.3)	NA	NA	NA	6/6 (100.0)
No previous use	NA	135/651 (20.7)	NA	NA	NA	–
Healthcare professionals' specialty ‡‡, n/N (%)						
Medical doctor	NA	NA	NA	29/56 (51.8)	NA	3/3 (100.0)
Nurse	NA	NA	NA	5/56 (8.9)	NA	–
Nutritionist	NA	NA	NA	4/56 (7.1)	NA	–
Pharmacist	NA	NA	NA	3/56 (5.4)	NA	–
Psychologist	NA	NA	NA	1/56 (1.8)	NA	–
Other	NA	NA	NA	14/56 (25.0) §§	NA	–
Healthcare professionals' experience in MS, n/N (%)						
Extensive/some	NA	NA	NA	45/58 (77.6)	NA	3/3 (100.0)
No experience	NA	NA	NA	13/58 (22.4)	NA	–
Healthcare professionals' experience in complementary therapies, n/N (%)						

Continued

Table 2 Continued

	COS survey					COS consensus meeting
	Total sample	People with MS	Relatives/ friends	Healthcare professionals	Researchers	
	n=770*	662 (86.0%)	27 (3.5%)	58 (7.5%)	23 (3.0%)	n=13 †
Extensive/some	NA	NA	NA	40/58 (69.0)	NA	2/3 (66.0)
No experience	NA	NA	NA	18/58 (31.0)¶¶	NA	1/3 (33.0)

We performed an available case analysis (participants not providing any answer to a particular item were excluded from the denominator and numerator).
*Participants that consented to participate, defined their role and answered at least one outcome (that is, rated the outcome or answered 'Unable to respond').
†Consensus meeting participants' roles: pwMS (n=6; 46.1%); friend of pwMS (n=1; 7.7%); healthcare professionals (n=3; 23.1%) and researchers (n=3; 23.1%).
‡Other countries (n, total sample): Belgium,[2] eg,ypt,[2] Greece,[2] Liechtenstein,[2] Saudi Arabia,[2] Sweden,[2] Argentina,[1] Australia,[1] Canada,[1] Chile,[1] India,[1] Israel,[1] Luxembourg,[1] Portugal,[1] Romania,[1] Seychelles,[1] Tunisia,[1] UK.[1]
§Other countries of residence for pwMS (n): Belgium,[1] Greece,[1] Liechtenstein,[2] Sweden,[2] Luxembourg,[1] Portugal,[1] Romania,[1] Seychelles.[1]
¶Other countries of residence for relatives and friends (n): Egypt.[1]
**Other countries of residence for healthcare professionals (n): Argentina,[1] Chile,[1] Saudi Arabia,[1] UK.[1]
††Other countries of residence for researchers (n): Australia,[1] Belgium,[1] Canada,[1] Egypt,[1] Greece,[1] India,[1] Israel,[1] Saudi Arabia,[1] Tunisia.[1]
‡‡Each respondent could choose only one specialty. One respondent defined himself as an MS neurologist who is active in research and a person living with MS. He chose the option healthcare professional: medical doctor.
§§Other healthcare professionals (alphabetical order): acupuncturist,[1] chiropractor,[1] craniosacral therapist,[1] complementary therapist,[3] Feldenkrais therapist,[1] health coach and BSc in Nutrition & Dietetics,[1] homoeopath,[2] nurse and reflexology therapist and lymph therapist,[1] nurse specialised in integrative medicine,[1] speech therapist,[1] staff member at palliative care organisation,[1] retired (profession not detailed).[1]
¶¶One health professional did not answer to experience in complementary therapies. It was assumed that this health professional had no experience in this field.
COS, core outcome set; MS, multiple sclerosis; pwMS, people with multiple sclerosis; Q, quartile.;

the outcome 'bladder problems', which was rephrased to 'bladder and prostate problems'.

COS consensus meeting

The study management team invited 66 individuals (44 pwMS, four relatives or friends, nine healthcare professionals and nine researchers) to select one of four time slots for the consensus meeting. The time slot with the highest availability of individuals was chosen. 13 participants attended the meeting on 25 June 2024, including pwMS (n=6, 46.1%), a friend of a pwMS (n=1, 7.7%), healthcare professionals (n=3, 23.1%) and researchers (n=3, 23.1%). See their characteristics in table 2.

Before voting, the discussion on outcomes without consensus centred on how an outcome's prevalence impacts its importance rating. It was noted that even if an outcome is not prevalent, its severity can still render it very important. Additionally, participants discussed that an outcome might be rated less important if it is a secondary effect of another outcome, such as sexual problems resulting from depressive mood.

Following the voting on the 21 survey outcomes without previous consensus, seven outcomes were added to the 'consensus in' in the COS, four met the criteria for 'consensus out' and 10 outcomes were still classified as 'no consensus'.

After the voting, the discussion addressed outcomes that remained unclear. Participants noted that an outcome might be considered not relevant for pwMS if MS is not the primary cause of the problem. For example, sleep problems could be more closely associated with other factors, such as age, daily habits, etc, rather than specifically MS.

The COS arising from the consensus meeting included 20 outcomes across nine domains. For 10 additional outcomes, there was still no consensus on whether to include or exclude (table 3 and online supplemental file 7).

Final stakeholder advisory board meeting

The six stakeholder advisory board members attended a 1-hour meeting on 4 July 2024. Revising the excluded outcomes, the decision was made to include sexual problems in the COS, despite its previous exclusion in the COS survey, due to its relevance especially for the younger generation and potential underreporting. The meeting participants confirmed the exclusion of the other outcomes previously excluded (low appetite, nausea/vomiting, hearing problems, safety of cannabis, mitigation of conventional medicine side effects, gastric problems, breathing problems and epileptic attacks).

Concerning the 10 outcomes without previous consensus, the stakeholder advisory board proposed the inclusion of nine (depressive mood, emotional lability, sleep problems, memory problems, urinary tract infections, visual problems, speech problems, dysphagia and safety of complementary therapies). These outcomes were deemed as prevalent or had a high impact on pwMS. The Uhthoff phenomenon was not considered a priority and, thus, was excluded from the COS, as it can generally

Table 3 Outcomes ratings

	COS survey (n=770)	COS consensus meeting (n=13)	Final SAB meeting (n=6)	Final COS
I MS activity				
1. MS clinical relapses	🟢	–	–	🟢
II Mental health				
2. Anxiety	⚫	🟢	–	🟢
3. Depressive mood	⚫	⚫	🟢	🟢
4. Emotional lability	⚫	⚫	🟢	🟢
III Cognitive function				
5. Attention and concentration	⚫	🟢		🟢
6. Memory problems	⚫	⚫	🟢	🟢
IV Sensory and pain				
7. Pain	🟢	–	–	🟢
8. Hearing problems	🔴	–	–	🔴
9. Visual problems	⚫	⚫	🟢	🟢
10. Sensory problems	⚫	🟢	–	🟢
11. Uhthoff phenomenon	⚫	⚫	🔴	🔴
V Neurological problems				
12. Epileptic attack	⚫	🔴	–	🔴
13. Dizziness and vertigo	⚫	🟢	–	🟢
VI Muscular problems				
14. Muscular weakness	🟢	–	–	🟢
15. Paralysis	🟢	–	–	🟢
16. Spasticity/tremor/spasms	🟢	–	–	🟢
17. Gait/mobility problems	🟢	–	–	🟢
18. Balance problems	🟢	–	–	🟢
19. Dexterity problems	⚫	🟢	–	🟢
20. Speech problems	⚫	⚫	🟢	🟢
21. Breathing problems	⚫	🔴		🔴
VII Gastrointestinal problems				
22. Low appetite	🔴	–	–	🔴
23. Nausea/vomiting	🔴	–	–	🔴
24. Dysphagia	⚫	⚫	🟢	🟢
25. Gastric problems	⚫	🔴	–	🔴
26. Bowel problems	⚫	🟢	–	🟢
VIII Urinary problems				
27. Bladder and prostate problems	🟢	–	–	🟢
28. Urinary tract infections	⚫	⚫	🟢	🟢
IX Overall well-being				

Continued

Table 3 Continued

	COS survey (n=770)	COS consensus meeting (n=13)	Final SAB meeting (n=6)	Final COS
29. General quality of life	●	–	–	●
30. Health-related quality of life	●	–	–	●
31. Ability to work/perform daily activities	●	–	–	●
32. Emotional well-being	●	–	–	●
33. Fatigue	●	–	–	●
34. Sexual problems	●	–	●	●
35. Sleep problems	●	●	●	●
36. Social well-being	●	●	–	●
X Treatment-related outcomes				
37. Safety of complementary therapies	●	●	●	●
38. Safety of cannabis-based medicines	●	–	–	●
39. Mitigation of conventional medicine side effects	●	●	–	●

Colour codes for survey consensus: ●: consensus in. ●: consensus out. ●: no consensus. - : not assessed in that meeting.
*The study management team decided to rephrase "Bladder problems" as "Bladder and prostate problems" following a survey participant's suggestion to include prostate problems in the COS.
COS, core outcome set; SAB, stakeholder advisory board.

be prevented by avoiding situations that increase body temperature or can be managed by cold exposure, such as by a cool shower, cooling vests or antipyretic drugs. Ultimately, all participants in the stakeholder advisory board meeting agreed on the final COS.

Phase 5: Final COS development

Table 4 presents the final COS for trials on complementary therapies in pwMS, which includes 30 outcomes, divided into 10 domains.

DISCUSSION

Summary of main results

We developed a COS containing 30 outcomes relevant to pwMS, relatives and friends, healthcare professionals and researchers for use in RCTs of complementary therapies for adults with MS. Our COS was developed following a five-phase participatory research project comprising a scoping review, an international COS survey and two online consensus meetings.

Developing a COS for complementary therapies in pwMS was challenging. First, complementary therapies encompass a wide range of practices (ranging from mind-body interventions, physical applications, supplements and acupuncture) and potentially relevant outcomes. This diversity makes it more challenging to create standardised outcomes that are applicable across all these varied practices. Second, pwMS, healthcare professionals and researchers may have differing opinions on which outcomes are most relevant. pwMS may prioritise quality of life and symptom relief, while researchers might focus on more specific measurable outcomes. Interestingly, the ratings stratified by the stakeholder group did not identify relevant discrepancies among those groups. Third, complementary therapies may lack the robust scientific evidence that supports pharmacological treatments, leading to scepticism about the validity of a COS in this field. Nevertheless, highlighting the benefits of a COS in improving the consistency and quality of research on complementary therapies can provide broader acceptance of upcoming research results.

Strengths and limitations of this study

This study presents several strengths. First, adhering to recognised methods and reporting guidelines ensured a relevant and high-quality COS.[15 22 23] Moreover, our COS survey was methodologically sound. The survey tool randomised the order of outcome blocks, preventing participants from assigning undue importance to outcomes based on their position and, thus, enhancing the validity of the results.[44] Additionally, each outcome rating included an 'unable to respond' option, allowing respondents to opt out without guessing on an outcome they may not know, thereby maintaining data accuracy and likely reducing the amount of missing data. Finally, participants who did not respond or chose 'unable to

Table 4 Final COS for trials of complementary therapies in pwMS

Domain	Outcome
I. MS activity	1. MS clinical relapses
II. General issues	2. Fatigue 3. Sleep problems 4. Dizziness/Vertigo 5. Sexual problems
III. Mental health	6. Anxiety 7. Depressive mood 8. Emotional lability
IV. Cognition	9. Attention and concentration problems 10. Memory problems
Pain and sensory	11. Pain 12. Visual problems 13. Sensory problems
VI. Neuromuscular	14. Muscular weakness 15. Paralysis 16. Spasticity, tremors or spasms 17. Gait and mobility problems 18. Balance problems 19. Dexterity problems 20. Speech problems
VII. Gastrointestinal	21. Dysphagia 22. Bowel problems
VIII. Urinary	23. Bladder and prostate problems 24. Urinary tract infections
IX. Overall well-being	25. General quality of life 26. Health-related quality of life 27. Emotional well-being 28. Ability to work or perform daily activities 29. Social well-being
X. Treatment-related outcomes	30. Safety of complementary therapies

MS, multiple sclerosis.

respond' were not considered for the analysis of that outcome. This approach provided a more precise estimation of the importance of each outcome as it focused on clear opinions.

Second, our COS integrated perspectives aligned with real-world needs,[15 45 46] by ensuring that pwMS were adequately represented throughout every step. 85% of the 770 respondents in our international COS survey were pwMS, making it the most representative of any other COS on MS published in the last 10 years, involving a maximum of 34 pwMS.[18–20] Our survey sample included 77.3% female participants with a mean age of 50.3 years. This closely aligns with recent data from the Swiss Multiple Sclerosis Registry, which reported 74.1% female participants and a mean age of 52.8 years.[47] These similarities suggest that our sample is representative of the national MS population in Switzerland in terms of gender and age. Comparable demographic patterns have been observed in other Western countries.[48] Moreover, at the COS consensus meeting, pwMS and their relatives/friends made up about half of the participants. Additionally, a pwMS in our stakeholder advisory board, overseeing the full project, and our consensus criteria, prioritising the perspectives of pwMS through a strict threshold for inclusion of each outcome, ensured that the views of pwMS were adequately represented. Concerning the 58 healthcare professionals participating in the COS survey, 78% were experienced in managing MS and 69% in complementary therapies.

Third, our COS survey was multilingual (English, German, French, Italian, Spanish), enhancing its inclusivity.[49] Fourth, we conducted all our meetings online, which offered an array of benefits: (a) increased accessibility and inclusivity by allowing diverse participation regardless of location; (b) lower cost and reduced environmental impact by eliminating travel and accommodation expenses; (c) convenience and efficient use of time and (d) enhanced documentation through easy recording and the use of real-time collaboration tools.

This study also presented limitations. First, the survey instructions provided examples of complementary therapies but did not include a comprehensive list of eligible and ineligible interventions. This shortage of detail posed challenges, including the lack of specificity and potential misinterpretations. Different respondents may have considered certain therapies but not others, potentially overlooking relevant therapies because they were unaware of them. Despite these drawbacks, our approach offered flexibility, increased participation and captured diverse perspectives, enhancing the real-world relevance of our findings. Another reason for not providing a comprehensive list is the lack of clear agreement on what constitutes complementary therapies.

Second, our COS survey predominantly collected responses from Switzerland, which limits the generalisability of our survey findings to a broader international context. The sample surveyed in our COS appears representative of the European MS population as 86% of the respondents were pwMS, 95% of them lived in Europe and were predominantly women (75.3%) with a mean age of 50.3 years (SD 12.2). Cultural and healthcare system differences, also in the use and definition of, and access to complementary therapies, may influence the perceived importance of the outcomes. However, our COS consensus meeting included participants from high-income or upper-middle income level countries other than Switzerland, such as the USA, Italy, Iran and Mexico.[50] Such diverse international participation to the consensus meeting provided some level of cross-cultural insight across countries with different economic settings despite the initial geographical concentration. Some decisions, such as excluding the Uhthoff phenomenon from the COS because it can typically be prevented by avoiding situations that raise body temperature, may be biased towards high-income settings. In lower-income contexts, avoiding such situations may be more challenging due to limited access to resources like

air conditioning. This highlights the need for greater consideration of diverse socioeconomic environments in these decisions.

Third, the COS survey shows a relative under-representation of healthcare professionals (7.5%) and researchers (3%) among respondents. To reach them, we implemented targeted invitation strategies, specifically by sending personalised email invitations to authors of the studies included in our scoping review. However, this under-representation likely did not affect the perspectives used to develop the COS, as healthcare professionals and researchers were actively involved in the consensus meetings and the stakeholder advisory board, ensuring a balanced and comprehensive finalisation of the COS.

Fourth, due to the primary method of disseminating the survey being through newsletters, we could not determine the total number of individuals reached or the proportion who participated. Still, the large number of respondents (n=770) provides a large and diverse sample. Most respondents were pwMS (86%), but all stakeholder groups were represented, including healthcare professionals, researchers and relatives or friends. Participants resided in 26 countries, with the majority based in Switzerland (88%), providing national depth and some international diversity. The sample showed variation in gender (75% women, 24% men, 1% other) and age (median 51 years; IQR 41–60). Prior use of complementary therapies was reported by 79% of pwMS. This composition enhances the credibility of our findings, though limitations in geographical representativeness remain, as few participants from low-income countries contributed to the study.

Fifth, selection bias may have affected the survey responses since over one third of the individuals accessed the survey through the channels of patient or professional organisations. In particular, pwMS who are part of patient organisations may only partially represent the broader MS patient population, as they typically have higher engagement with their health and better access to information. They may also differ in socioeconomic status and healthcare access compared with non-members. While their insights are valuable, their experiences might not fully reflect the diversity of all MS patients. However, all pwMS face a chronic disease for which there is no cure, making them willing to try other therapies that offer potential improvement. As a result, the pwMS recruited for our survey may not differ significantly from others in their use of, or expectations for, complementary therapies. Besides, the online procedures used in the study, while allowing the researchers to reach a broad number of participants, may also prevent the representation of users who do not feel comfortable with technology, for various reasons. One more possible reason for selection bias may be the online nature of the survey, potentially over-representing pwMS with easier access to the Internet and digital technology. However, both these potential risks of selection bias were weighted and balanced towards cost-opportunity and feasibility issues in trying to reach a broader, highly representative population of stakeholders.

Sixth, the COS proposes 'what' outcomes to consider but does not recommend 'how' (which tools are optimal to measure each of these outcomes) and 'when' (at which time-point) to measure these outcomes. Further research and consensus processes are typically required to determine these aspects, which were beyond the scope of our project's timeline.

Finally, the large dropout between users who accessed the survey (n=1900) and those who completed outcome ratings (n=602) warrants attention. This attrition occurred primarily at the introduction page (991 users, 76.3% of all dropouts), before reaching the informed consent page. High early attrition is common in open online surveys without personal invitations, especially those widely disseminated via newsletters and social media. Many recipients may lack interest in the topic, be uncertain about eligibility or have privacy concerns. These factors have been identified as relevant to early postconsent attrition in online surveys.[51–53] Although this self-selection may have introduced bias, the substantial number of respondents and the transparent recruitment process help support the credibility of the final sample. Further research is needed to understand preconsent dropout, such as through exit questions or follow-up inquiries.

Comparison with prior work

To our knowledge, this is the first COS focusing on complementary therapies for pwMS. While it was tailored to this population and interventions, it included outcomes also relevant to other health areas, such as Parkinson's disease, post-COVID condition or pharmacological interventions for MS.[18–21 37] This overlap stems from shared therapeutic goals, the importance of general health and well-being and the need to manage common symptoms such as fatigue. By incorporating our outcomes, we ensure that our research is tailored to MS and complementary therapies.

Implications for practice and future research

Implications for practice: use of the COS

This COS should be regarded as a minimum set of outcomes to be collected in RCTs evaluating the effects of complementary therapies in pwMS. We do not recommend including all these outcomes in a single study, as their relevance may vary based on the specific complementary therapy being evaluated. For instance, outcomes like muscular weakness may be more pertinent for physical therapies such as yoga or exercise programmes, while emotional well-being may be more relevant for mindfulness practices. Besides, we acknowledge that, due to the holistic and multimodal nature of many complementary therapies, these aim to improve overall well-being or affect multiple domains simultaneously—such as physical symptoms, emotional state and quality of life—making outcome selection inherently complex. Our COS

addresses this challenge by offering a broad yet structured set of outcomes, allowing researchers to select those that best reflect the intervention's scope and intended effects. This flexibility supports the pragmatic application of the COS across diverse complementary therapy modalities.

This COS is also applicable to other evaluative study designs, including non-randomised trials, observational studies and systematic reviews. Thus, it represents a significant advancement in improving evidence synthesis related to MS and complementary therapies.

Given the potential wide range of complementary therapies relevant to pwMS, we chose not to impose strict requirements for including outcomes in our COS. As a result, the COS contains a comprehensive list of outcomes.

This study is part of the PEMS project: *Participatory Evidence Synthesis in Multiple Sclerosis and complementary therapies*. PEMS is a 2-year project funded by the Swiss MS Society.[54] Our COS will be integrated into a free interactive online evidence and gap map. This map will collate the RCTs and systematic reviews evaluating the effects of complementary therapies on the COS in pwMS. We will engage with different organisations to disseminate the map and reach a wider interested public.

Implications for future research

Responders were primarily based in European high-income countries, which raises concerns about the COS's applicability in non-European contexts and countries with lower income. To address this issue, future COS research should include participants from other geographical regions, including low- and middle-income countries, where perspectives and access to complementary therapies may vary. This could help assess whether the importance of outcomes varies by context, ensuring a broader relevance.

Our team initially planned to use the 1–9 point scale proposed by the GRADE Working Group,[55] along with an 'it varies' option for rating the importance of each outcome. This option is particularly useful for capturing the complexity of symptoms in pwMS, which may change over time. However, our consultations with stakeholders indicated that these options were challenging to apply. Additionally, a study comparing rating scales in COS development studies concluded that the three-point scale 'proves to be the most reasonable choice, as its translation into the clinical context is the most straightforward among the scales'.[56] Therefore, further research is needed to determine the most appropriate scale for rating the importance of outcomes.

During the meetings, there were discussions on how to measure potential outcomes, such as emotional lability, and whether this should influence the rating of their importance. However, it was clarified that the study's aim was to agree on 'what' should be measured, rather than 'how' and 'when'. Now that the COS has been established, further research is needed to reach consensus on which tools are optimal to measure each of these core outcomes and at which time-point

MS symptoms and their progression vary greatly among individuals, complicating the creation of a COS that is neither too broad nor too specific. A stratified approach, where outcomes are tailored to different stages or types of MS, might be necessary.

CONCLUSIONS

This study developed the first COS applicable for future trials of complementary therapies for pwMS. This COS identified the relevant outcomes among pwMS, relatives and friends, healthcare professionals and researchers. We recommend that researchers designing trials of complementary therapies consider this COS, as it may help reduce the gap between research and clinical practice by promoting the consideration of outcomes relevant to key stakeholders. This COS strengthens the foundation for integrating complementary therapies into holistic MS management where appropriate. Future work is needed to assess the generalisability of the COS across diverse settings.

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Contributors CMW and JL-A conceived this study. AKT, CMW, CC, JB, JL-A and YY were part of the study management team. CB, GR, NS, SB, SH-L and VvW were part of the PEMS project stakeholder advisory board. JL-A and CMW designed the study. JL-A wrote the study protocol. AKT, CB, CC, CMW, GR, JB, NS, SB, SH-L, VvW and YY read the protocol critically and approved its final version. AKT, JLA and YY performed the scoping review. AKT, CMW and JLA developed the survey. AKT, CC, JLA and NS were involved in the survey translations. AKT implemented the survey in SoSci Survey and ran the analyses. JL-A and JB supervised data analysis. JB and CMW facilitated the COS consensus meeting and the stakeholder advisory board meeting, respectively. AS, FN, FP, HK, IPN, JK, LSW, US-M and XW participated in the COS consensus meeting. CB, GR, NS, SB, SHL and VvW participated in the final SAB meeting. JLA drafted the manuscript. All authors (AKT, AS, CB, CC, CMW, FN, FP, GR, HK, IPN, JB, JK, JLA, LSW, NS, SB, SHL, US-M, VvW, XW and YY) reviewed and provided comments on the manuscript. CMW obtained funding for this project. CMW accepts full responsibility for this work and acts as guarantor. ChatGPT and Grammarly were used for writing assistance. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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