BMJ Open

Development of a core outcome set of clinical research on the integration of traditional Chinese and Western medicine for spinal metastases: a study protocol

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To cite: Fang G, Yu W, Chen D, *et al*. Development of a core outcome set of clinical research on the integration of traditional Chinese and Western medicine for spinal metastases: **a study protocol**. *BMJ Open* 2024;**14**:e083315. doi:10.1136/bmjopen-2023-083315

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-083315).

GF and WY are joint first authors.

Received 17 December 2023
Accepted 27 August 2024

Check for updates

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ABSTRACT

Background In recent years, the incidence of spinal metastasis (SM) has been increasing steadily. In response to this serious public health problem, researchers have made progress by using the integration of traditional Chinese and Western medicine. However, considerable heterogeneity in the definition and measurement of outcomes across clinical research studies, along with the lack of uniform measurement standards for study data, makes it difficult for researchers to compare different treatments. Therefore, it is crucial to accurately evaluate clinical research on the integration of traditional Chinese and Western medicine for SM.

Methods This study protocol outlines a comprehensive research programme based on the Core Outcome Set Standards Protocol Items. The study consists of four phases: a literature review, semistructured interviews, a two-round modified Delphi survey, a consensus meeting. Phase 1 involves a comprehensive literature review to extract outcomes used in current clinical studies of integrated traditional Chinese and Western medicine or Western medicine for the treatment of SM. A semistructured interview format will be used to survey patients and caregivers in phase 2 to collect suggestions from the patient perspective. Phase 3 involves a two-round modified Delphi survey to complete a prioritisation evaluation of outcomes to generate a candidate list for core outcome set (COS). Finally, phase 4 involves a face-to-face consensus meeting to review and establish the COS.

Ethics and dissemination Conducted in response to the current dilemma of SM, the study was endorsed by the Spine Oncology Group of the Orthopaedic Surgeons Branch of the Chinese Physicians' Association. It will be developed and reported through a rigorous process, with the results of the study to be published in a peer-reviewed journal.

Registration: COMET Registry: COMET 2938; https://www.comet-initiative.org/Studies/Details/2938.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol is the first core outcome set (COS) registered on the Core Outcome Measures in Effectiveness Trials website for the treatment of spinal metastasis through Traditional Chinese Medicine (TCM) or integrative medicine.
⇒ The study will be developed using a mixed-methods approach that included literature reviews, patient interviews, Delphi surveys and a consensus meeting.
⇒ The study will provide a feasible programme for clinical researchers to facilitate the integration of research data and improve the quality of research.
⇒ The primary use of TCM or integrated medicine is in China. Therefore, geographical limit the applicability of this COS.

INTRODUCTION

Spinal metastasis (SM) occurs as a complication in the advanced stages of malignant tumours, with a prevalence ranging from 40% to 70%. SM can cause vertebral fractures, nerve compression and impairment of spinal stability and result in pain, neurological dysfunction, motor function loss and even paralysis.[1–7] The complexity of the underlying condition and the high heterogeneity of the primary tumour in patients with SM make clinical management extremely difficult. Considering the intricate nature of symptoms exhibited by patients with SM and the challenges associated with clinical management, scholars have recommended multidisciplinary treatment (MDT) for the clinical management of SM. Conventional MDT employs a variety of interventions, including surgical interventions, radiation therapy, holistic treatments, bone preservation strategies and analgesics.[2 3 8–11] Consequently,

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various treatment decision-making frameworks have been developed.[2 10 12]

MDT has a unique interpretation in China that encompasses not only multidisciplinarity but also the integration of two medical philosophies. The integration of Traditional Chinese Medicine (TCM) and Western Medicine (WM) has achieved remarkable results in the treatment of cancer.[13–16] TCM has a unique perspective and a well-established framework in the field of oncology. Studies have shown that TCM has significant therapeutic effects on patients with advanced tumours, effectively reducing the adverse effects of systemic therapeutic drugs while improving the body's ability to recover and its tolerance of treatment. [15 17 18] Frailty can be fatal to oncologic diseases, including SM, which can severely affect a patient's ability to tolerate treatment.[19–21] Studies have shown that when patients are severely weakened, herbs can slow weight loss, enhance muscle mass and improve poor nutritional status caused by poor sleep quality and loss of appetite.[22 23] Therefore, the addition of TCM before and after Western medical treatment, as well as during drug rest periods, is a promising therapeutic approach. For patients with SM, the integration of TCM and WM has the potential to maintain treatment continuity and improve quality of life, and it shows a broad application prospect. However, a noteworthy challenge is the lack of a standardised efficacy evaluation system for TCM treatment. This challenge is reflected in the strong substitutability and subjectivity of outcomes, the lack of clarity in the selection of endpoint indicators and the ambiguity of measurement time.[24 25]

In summary, the precise curative effect of various treatment techniques outlined in clinical management guidelines and systematic reviews on SM are unclear.[26–31] The reason for this limitation stems from the severity and complexity of SM, which makes conducting high-quality studies such as randomised controlled trials difficult. Another dilemma in this context is the wide variation in the definitions and specific measurements of the outcomes chosen for clinical research, which diminishes the measurability of the results and does not provide an effective guide for clinical decision-making.[32–34]

The core outcome set (COS) represents the minimum set of crucial and standardised outcomes used for assessing and reporting in all effectiveness trials within a specific clinical area.[35] The introduction of COS presents a viable solution to address the discrepancies observed in clinical research outcomes. The Core Outcome Measures in Effectiveness Trial (COMET) initiative was established to improve the consistency of the outcome selection in research design, promote the integration of clinical data and enhance the grade and value of clinical research evidence.[36] In recent years, COS studies have been conducted by international scholars, playing pivotal roles across diverse disease domains.[37–39] Similar to many studies, the question of 'what' the most critical outcomes are is central to improving the research quality of clinical studies on SM. COS is a critical step in clarifying what to measure in clinical research, thus providing an effective solution to the problem. Therefore, to optimise the efficacy evaluation system and more clearly demonstrate the effectiveness and advantages of intervention measures, it is necessary to develop a COS for clinical research on SM.

The aim of this study is to develop a COS applicable to clinical research on the integration of Traditional Chinese and WM in the treatment of SM. We aim to identify a short list of important outcomes that must be assessed in all relevant clinical researches, defining the 'what' that needs to be measured.

This will determine the important outcomes that clinicians and researchers need to report in clinical studies involving TCM or integrated Traditional Chinese and WM in the treatment of SM. This protocol follows the Core Outcome Set Standards Protocol Items (COS-STAP Statement).[40]

METHODS

Steering committee

A steering committee will be established to review and approve the research plan, monitor the progress of the research, resolve differences and review the final research results. The steering committee will consist of seven experts from China. Senior researchers from various fields were invited to participate in the study through expert recommendations made by societies and physician organisations. Following thorough communication and consultation, one of the experts will be appointed as the chairperson.

The experts will include: (1) A TCM orthopaedic and traumatology clinician with an MD degree and a title of associate senior or above, with more than 5 years of work experience in a tertiary hospital; (2) a WM clinician in spine surgery with an MD degree and a title of associate senior or above, with more than 5 years of work experience in a tertiary hospital; (3) a TCM clinician in oncology with an MD degree and a title of associate senior or above, with more than 5 years of work experience in a tertiary hospital; (4) a WM clinician in oncology with an MD degree and a title of associate senior or above, with more than 5 years of work experience in a tertiary hospital; (5) a radiology clinician with an MD degree and a title of associate senior or above, with more than 5 years of work experience in a tertiary hospital; (6) a clinical researcher with an MD degree and at least 5 years of research experience related to SM; (7) methodologist with a PhD and at least 5 years of medically related research experience.

In addition, a patient representative will be invited to participate, which will help ensure that patients understand the development process and results as well as provide suggestions from a patient perspective. The patient representative will be selected from the SM patient support organisation at the study enrolled hospitals and will be elected by patient votes.

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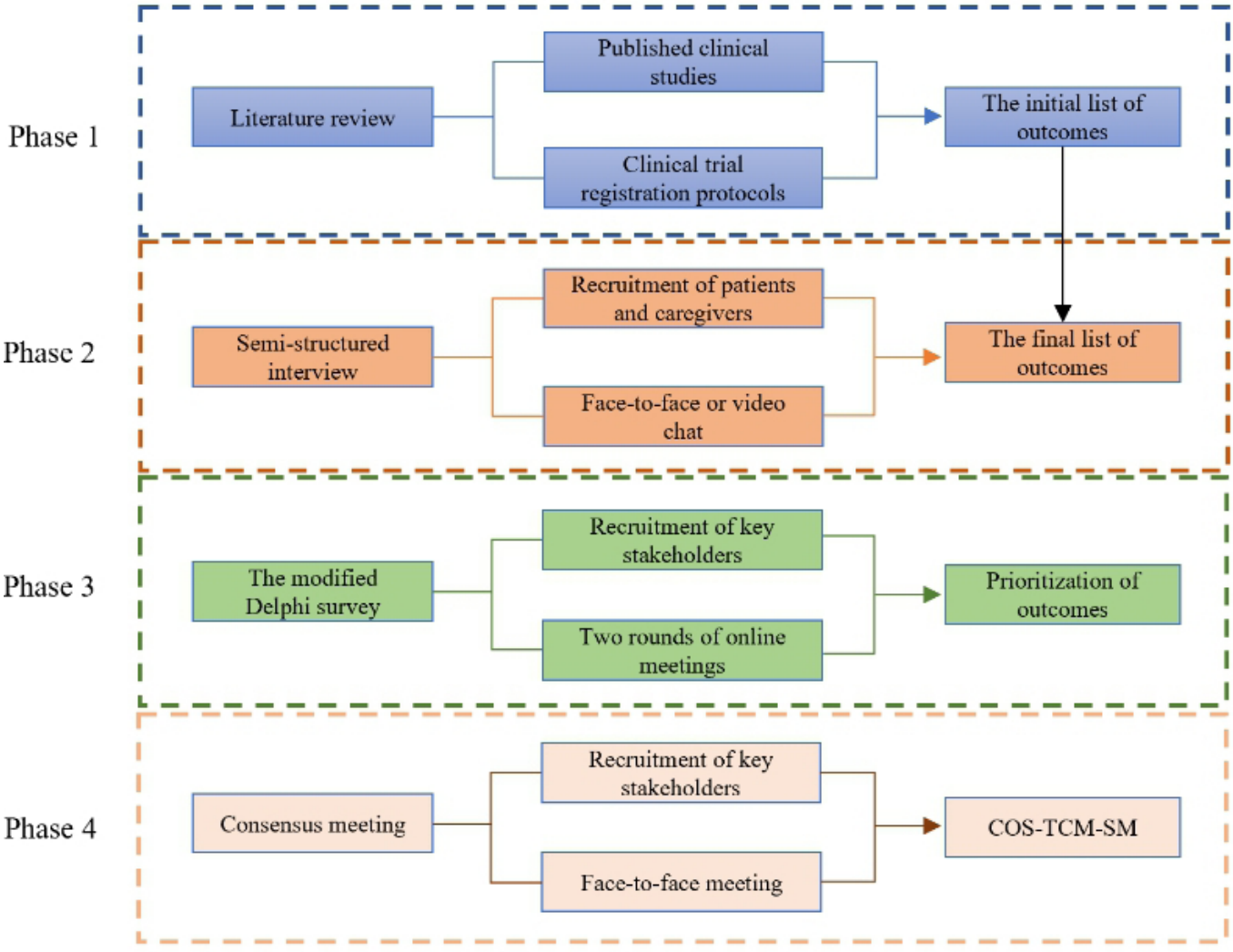

Figure 1 Study flow chart of the protocoll. COS, core outcome set; SM, spinal metastasis; TCM, Traditional Chinese Medicine.

Working group

A working group will be established to distribute questionnaires, analyse results and organise meetings at all stages of the research. The working group will consist of nine members, including two professors, one TCM clinician, one WM clinician, two methodologists and three graduate students, all from China.

Study design

The protocol was developed in accordance with the COS-STAP[40], as detailed in online supplemental file 1. The study will be implemented based on the COS-STAD,[41] and the research process will refer to the COS-Handbook.[35] This project will be carried out from July 2024 to May 2025. The study will be divided into four phases (figure 1): a literature review, semistructured interviews, a two-round modified Delphi survey and a consensus meeting.

Phase 1: to Conduct a literature review and extract the outcomes to form an initial list of outcomes through induction and classification.

Phase 2: gather patient perspectives through semistructured questionnaires and synthesise opinions to produce a comprehensive list of outcomes.

Phase 3: conduct a two-round modified Delphi survey and invite key stakeholders to prioritise the outcomes.

Phase 4: organise a consensus meeting to review the results and establish the COS.

Phase 1: literature review

During this phase, the working group will conduct a literature review of clinical research reports and registration schemes of TCM, WM or integrated medicine for SM. Given the complexity of the SM, we will also collect relevant grey literature, including academic conference proceedings, technical reports and medical brochures to ensure the comprehensiveness of the outcomes. The working group will then extract the outcomes from all studies and subsequently categorise and standardise them according to the COMET handbook's classification framework for outcomes (online supplemental file 2).[35]

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Table 1 Inclusion and exclusion criteria of systematic review

Items	Inclusion criteria	Exclusion criteria
Patients	Patients (age≥18 years) with a definitive diagnosis of SM	Patients with other complications or acute internal medicine diseases
Intervention	One or more interventions related to TCM or integrative medicine	Purely Western medical treatments
Outcome	Outcomes with clear definitions and specific measurements, including safety and efficacy	Unclearly defined outcomes or unclear measurements
Study types	effectiveness clinical studies, types include randomised controlled trials, non-randomised controlled trials, cohort studies, observational studies and case–control studies	Non-effectiveness clinical studies or non-primary clinical studies, including basic studies, cadaveric studies, reviews, systematic reviews, commentaries and letters or research aimed at validating mechanisms of interventions or other purposes
Language	Chinese and English	Published in languages other than Chinese and English

SM, spinal metastasis; TCM, Traditional Chinese Medicine.

Following evaluation by the steering committee, an initial list of outcomes will be generated.

A systematic review of published original clinical studies

Search strategy

Eight electronic databases will be searched, including English databases (PubMed, Embase, Cochrane Library and the Web of Science) and Chinese databases (China National Knowledge Infrastructure, Wanfang Database, SinoMed and VIP information resource integration service platform database). The search period will be covered from the establishment of the database to 31 December 2023. The search strategy for the English databases was present in online supplemental file 3.

Inclusion criteria and exclusion criteria

The inclusion and exclusion criteria for published studies are presented in table 1. The following inclusion criteria will be used: (1) the study included patients (age ≥18 years) with a definitive diagnosis of SM; (2) interventions were treatments related to integrated TCM and WM; (3) the purpose of the study was to investigate the efficacy or safety of the intervention; (4) the study was an effective clinical studies, including randomised controlled trials, non-randomised controlled trials, cohort studies, observational studies and case–control studies; (5) the study had clear definitions and specific measures for the selected outcomes; (6) the language of study was Chinese or English.

The following studies will be excluded: (1) the study was conducted on patients who did not have a clear diagnosis of SM or were younger than 18 years of age; (2) studies involving patients with other complications or acute internal medicine diseases; (3) non-effective clinical studies, such as research aimed at validating mechanisms of interventions or other purposes; (4) studies with unclear definitions or measurements of the outcomes addressed; (5) non-primary clinical studies, including basic research, cadaveric studies, reviews, systematic reviews, commentaries and letters; (6) studies published in other language.

Literature selection and data extraction

Two reviewers will independently review the titles and abstracts of relevant studies and further screen them based on the full texts. Disagreements will be resolved through consultation or by review from a third reviewer. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart will be presented based on the screening process.[42]

Two researchers will independently extract and cross-validate the data. The extracted data will include (1) basic information about the studies, including the title, first author's name, publication date, area of implementation and ethical approval; (2) baseline characteristics of the patients, including sample size, age, primary malignant tumour, course of the disease, site of SM, involved segments of the vertebral body, involvement of spinal canal and TCM information (syndrome, symptom, tongue and pulse); (3) details regarding the intervention measures, including the modality of intervention (such as surgery, radiotherapy and pharmaceutical interventions) and as well as treatment duration, frequency and dosage; and (4) comprehensive details of the outcomes, including nomenclature or definition, measurement methods, specific time points and frequency of measurements.

Step 2: a review of clinical trial registration protocols

Search strategy

We will conduct a comprehensive search of the clinical trials.gov and Chinese clinical trials registries, covering the entire database history up to 31 December 2023, using 'SM' as the keyword.

Inclusion criteria and exclusion criteria

The inclusion and exclusion criteria for published studies are presented in table 1.

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Data extraction

The extracted data will include the country or region of trial registration, trial status, ethical approval, funding source, research stage, intervention measures, selected outcomes, outcome measurement methods, time points and frequency of measurements.

Step 3: form the initial list of outcomes

The working group will summarise and analyse the extracted outcomes. All disagreements will be resolved through discussion with a third reviewer. This step will be divided into three parts: (1) establish a comprehensive list of all extracted results using Microsoft Excel, labelling the sources and counting the frequencies; (2) eliminate redundant outcomes, standardise the naming of semantically equivalent outcomes and decompose composite outcomes. Domain classification will be performed according to the functional attributes of the outcomes,[43] while retaining unclassifiable outcomes; (3) conduct an assessment by a steering committee to consider the appropriateness of the categorisation of outcomes and to produce a preliminary list of outcomes.

Phase 2: semistructured interview with patients

Conducting patient interviews is a crucial aspect in the development of COS, as it allows for valuable insights and perspectives to be gathered from the patients involved in the project.[44–46] Studies have shown that semistructured interviews are a reliable and effective methodology.[47 48] Interviews will be conducted either offline face-to-face or via web chat, using a predesigned survey outline to collect opinions in a comprehensive manner. Suggestions from the patient's perspective will be analysed verbatim and incorporated into the initial list of outcomes.

Step 1: patients' semi-structured interview

Eligibility criteria

We intend to recruit patients with SM or their caregivers from Longhua Hospital affiliated with the Shanghai University of TCM, Shandong Hospital of TCM, Shanghai Changzheng Hospital and Fudan University Shanghai Cancer Center. Recruitment will be conducted through posters, patient organisations and online advertisements. Prior to the formal interviews, potential participants' online medical records and referral information will be reviewed by the working group to confirm that eligibility criteria are met. The process will be overseen by the steering committee and kept strictly confidential to protect patient rights. Participants recruited must fulfil the following criteria: (1) patients (age ≥18 years) with a definitive diagnosis of SM; (2) patients have received one or more of the integrated Chinese and WM treatments and (3) patients who are clearly aware and able to communicate independently.

Sampling

Previous COS research protocols and related studies have shown that semistructured interviews with 30–40 patients are effective in gathering patients' views and opinions.[49–51] Considering the intricate nature of SM and the numerous treatment approaches, a minimum of 100 patients will be recruited. After analysing the demographic characteristics of the enrolled patients, such as gender, age and treatment history, an internal evaluation will be conducted to assess the appropriateness of the recruitment methods used. If the patient cohort is under-represented, additional recruitment measures will be implemented.

Protection of participants

Members of the working group will be trained to safeguard patient emotions and communicate effectively during this phase. Prior to the interview, potential participants will be asked to voluntarily sign a basic information sheet and an informed consent form. We will emphasise that patients can opt out of the interview process at any time. An internal meeting of the steering committee finalised an outline for the interviews, which staff will use as a basis for conducting them. The outline of the semistructured interviews is shown in online supplemental file 4.

Step 2: construction of the final list of outcomes

Data analyses

Results of semistructured interviews completed at least 80% according to the outline will be considered valid. The interviews will be transcribed on paper and audio recorded, and the results will be reviewed during working group meetings. All differences will be resolved through internal meetings. The extracted outcomes will be adjusted according to the outcome classification method used in the first phase and compiled into the final list of outcomes after approved by the steering committee.

Phase 3: a two-round modified Delphi survey

The Delphi survey is an effective method for achieving group consensus through an iterative multistage process.[52 53] The working group will conduct a two-round modified Delphi survey through online meetings, recruit key stakeholder groups to assess the prioritisation of outcomes and reach an initial consensus on COS-TCM-SM.

Step 1: recruitment of stakeholders

Stakeholders will be recruited prior to the start of each round of the modified Delphi survey. Through a literature review and internal meetings, we identified four key stakeholder groups: (1) clinicians with a high degree of relevance to SM, such as spine surgeons, oncologists, radiotherapists, nurses and rehabilitation physicians; (2) researchers associated with SM, including medical device or drug developers, ethical reviewers, journal editors, methodology or statistics specialists; (3) policymakers, including healthcare managers and policymakers at different levels; (4) patients with SM who have received relevant treatment, and their caregivers. Clinicians, researchers and policymakers should meet the following criteria: they must have a doctoral degree and have worked in their area of specialisation for 5 years or more. Patients should fulfil the requirement of having received at least one or more interventions from TCM or the integrated

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Table 2 The 9-point Likert Scale

Score	Degree of importance
1–3	Limited importance
4–6	Important but not critical
7–9	Critical

TCM and WM. Although no research has established an ideal sample size for the modified Delphi survey, we aim to recruit 60 participants and allocate an equal quota to each group based on previous studies.[54–56] Recruitment of clinical workers will be conducted through advertisements on official hospital website, societies and physician organisation campaigns. Recruitment of investigators will be done through posters, web advertisements and steering committee recommendations. Decision-makers will be sourced from public officials at all levels of healthcare management recruited through electronic mail. Patients and caregivers will be sourced from patient organisations in each of the selected hospitals, and recruitment will be completed through offline outreach and posters. Electronic invitations will be distributed nationwide to stakeholders, providing contact information, study objectives, the abstract of the study and details for participation. To ensure a prompt response and minimise waiting time for participants, the recruitment process will be concluded within 30 days.

Step 2. scoring method and consensus criteria

The 9-point Likert Scale will be used as a stakeholder scoring tool. The tool was developed by the Grading of Recommendations Assessment, Development, and Evaluation Working Group and recommended by the COMET group.[57 58](Table 2) Scores of 1–3 indicate outcomes of limited importance, 4–6 indicate important but not critical and 7–9 indicate critical. A consensus on an outcome will be considered reached if ≥75% of stakeholders scored it 7–9 and ≤15% scored it 1–3. Conversely, if ≥75% of stakeholders score an outcome 1–3 and ≤15% score 7–9, the outcome will be ruled out.

Step 3: production of questionnaires

The results of the literature review and semistructured interviews will be compiled and analysed into a complete list. The working group will categorise the outcomes according to the domains of the outcomes and provide definitions and plain language understandings of each outcome. The order of the outcomes will be randomised for each questionnaire in order to avoid participants' first choice preferences. Both medical professional and lay versions of the questionnaire will be made available to lead to a full understanding of the content of the study by different groups.

Step 4: round 1

Implementation process

All potential participants will be required to provide personal information in the questionnaire attached to the invitation. For example, the patient group will be asked to include details regarding medical history, treatment process and future treatment plans. Clinicians, researchers and policy makers will need to provide information on their professional field, professional title and years of experience. The original documents will be securely stored to prevent leakage of personal information. The working group will carefully review the questionnaires to select the appropriate participants. Each candidate will be notified by phone or email. Participants will be asked to evaluate each item using the 9-point Likert scale. The questionnaire will conclude with two additional inquiries: (1) What additional outcomes do you believe should be incorporated into the questionnaire? (2 Do you find the content of the questionnaire to be reasonable? Please specify any aspects that seem unreasonable. Participants will be given 3 weeks to complete the online questionnaire, and in the final week, the working group will send a reminder.

On completion of round 1 of the Delphi survey, the working group will collect all questionnaires. The number of valid questionnaires (with more than 80% of questions answered), the average score for each outcome and the score distribution for each stakeholder group will be analysed. Participants' suggestions will be discussed internally and the potential meaningful outcomes will be incorporated into the questionnaire for round 2. Outcomes that receive a score of 7–9 from more than 75% of participants and a score of 1–3 from less than 15% of participants will be considered to have consensus importance and will be retained for round 2. Quantitative analyses will be conducted using STATA V.13. The overall mean score for each outcome and mean score for each stakeholder group for a single outcome will be calculated to assess differences in evaluation between the stakeholder groups.

Step 5: round 2

Implementation process

Stakeholders who validly completed the questionnaire in the first round will be eligible to participate in the second round. Details of round 1, including average scores for each outcome, differences in scores between stakeholder groups and a summary of opinions, will be made available to participants prior to the start of round 2. Participants will be required to grade the outcomes in the questionnaire using the same scoring criteria as in round 1. If participants change their scores for the same outcome between the two rounds, they will need to provide reasons. Participants will have 3 weeks to complete the questionnaire, the working group will send an email reminder before the final week deadline.

Mean scores and between-group differences will be calculated for the second round, and all outcomes were

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ranked according to their total scores. All calculations will be summarised in a report for review by the expert committee. Results that meet consensus criteria will be extracted, and results that fall between consensus and non-consensus will be reserved for discussion at the consensus meeting.

Phase 4: consensus meeting

Implementation process

A face-to-face consensus meeting will be convened to formulate and review the COS-TCM-SM. The 1-day meeting will take place in Shanghai, China and will be organised and chaired by the working group. Members of the steering committee will be eligible to vote during the meeting. The number of participants will be limited to 25, with participants randomly selected from each stakeholder group to reduce potential imbalances in representation.

Consensus meeting content

Prior to the start of the consensus meeting, a summary document describing the process and results of the previous study will be prepared to help participants familiarise themselves with the study. Based on the findings from the two-round modified Delphi survey, the working group will compile a list of core outcomes. Both medical professional and layperson versions of the questionnaire will be made available to lead to a full understanding of the content of the study by different stakeholder groups. After an anonymous voting process, any outcome with the consent of more than 80% of participants will be directly included into the COS. Outcomes receiving more than 20% of veto votes will be reconsidered. Any disagreements will be discussed and resolved by the steering committee. The measurement methods of the outcomes will be further discussed according to COS-SOMI.[59] Finally, a research report will be drafted for peer review following the COS-STAR statement.[60]

Patient and public involvement

None.

DISCUSSION

This study is the first COS study for SM. Our aim with this study was to define 'what' needs to be measured in a clinical trial of integrated TCM and WM for the treatment of SM. We anticipate disseminating the results to help clinical researchers standardise study procedures, improve study quality and increase the measurability of interventions for SM, thereby aiding medical decision-making and improving healthcare effectiveness.

The clinical management of SM has faced significant challenges. In this context, the establishment of a COS holds crucial clinical implications. Based on robust development standards, a four-phase research process comprising a literature review, semistructured interviews, a two-round modified Delphi survey and a consensus meeting will be employed for the development of COS-TCM-SM. The COS will help reduce heterogeneity and improve the value of TCM clinical researches involving patients with SM. Furthermore, the COS can enhance the evaluation of therapeutic effects during the treatment process, enabling the timely adjustment of treatment plans and improving clinical outcomes.[61]

Currently, although integrative medicine is a promising treatment modality, variability in the assessment of study outcomes makes it difficult to generalise findings.[62] COS provides an effective framework for the further development of integrated Chinese and WM treatments. Therefore, the development of a COS suitable for clinical trials of integrated Chinese and WM is imperative.

Through the preliminary work of this study, we found that the large differences between therapeutic interventions for SM similarly motivated investigators to develop specific COS, which may further guide the clinical management of SM. However, previous studies have demonstrated that the implementation of COS in clinics has not been ideal.[63–65] Therefore, ensuring the high-quality completion of research and the comprehensive promotion and application of the COS will be key areas of focus in the future.

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Contributors WY and GF initiated the collaborative project. DC, XD and LQ participated in the conceptualisation. LZ, XG and YY participated in manuscript preparation and review of the manuscript in several stages. QH, JM and MY approved the final version of the manuscript and the revisions as needed. WY and GF are co-first authors. WY and GF are co-response authors. The guarantor of the study is MY; accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The study was supported by the Project of Shanghai Municipal Health Commission (20204Y0165, 20224Y0165); National Natural Science Foundation of China (82205145); Shanghai 'Rising Stars of Medical Talents'—Youth Development Program-Youth Medical Talents-Specialist Program SHWSRS (2023-062); the Project of Chinese Society of Traditional Chinese Medicine youth talent lifting (2023-QNRC2-A03); the Project of Shanghai University of Traditional Chinese Medicine 'Visit famous schools and worship famous teachers' (079).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

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