· Methodology ·

Interpretation of the COMET Handbook (version 1.0) and its insight for developing core outcome sets in clinical trials of traditional Chinese medicine

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Abstract: A core outcome set (COS) is an agreed minimum set of outcomes that should be reported in all clinical trials in specific areas of health care. The use of COS can reduce the heterogeneity of outcomes reporting in different trials and make the systematic review or meta-analysis incorporate more research results for consolidation. It can also enhance the value of trials and reduce the waste of funds to some extent. Recently, Core Outcome Measures in Effectiveness Trials (COMET) Initiative has developed the COMET Handbook (version 1.0). This handbook discussed the current problems of COS research and made some recommendations. This paper interprets the COMET Handbook (version 1.0) and analyses its insight on the construction of traditional Chinese medicine clinical research COS, combined with the characteristics of traditional Chinese medicine clinical research, to provide a reference for related researchers.

Key words: The COMET handbook; Core outcome set; Traditional Chinese medicine; Clinical trial

The outcomes measured and reported in some similar clinical trials vary widely. Some clinical trials did not report the main outcome or did not report them completely [1,2]; some clinical trials report the outcome rarely, for example, the literature on the treatment of tumors shows that more than 25,000 outcomes appear only once or twice in clinical trials [3]. This phenomenon leads to many research outcomes that cannot be combined in the systematic review and can not provide a higher level of evidence to clinical practice. To a certain extent, this phenomenon reduces the value of research and result in waste [4]. Incomplete reporting of outcomes leads to the potential of selective reporting bias [5] and may lead to invalid or unfavorable application of interventions in clinical practice.

Core outcome sets (COS) are the key way to solve the problems mentioned above. A COS is an agreed minimum set of outcomes that should be reported in all clinical trials in specific areas of health care [6]. In 2010, the internationally renowned experts in the field of evidence-based medicine set up a work group named Core Outcome Measures in Effectiveness Trials (COMET). The aim of this work group is to build, implement, disseminate and update COS. In the same year, the work group of consensus-based standards for the selection of health measurement instruments (COSMIN) released the COSMIN list, the main aim of this work group is to evaluate the quality of related measurements in patient-report outcomes (PRO) [7]. In 2016, the COS-STAR Statement standardized COS reporting standards [8]; in the same year, COMET and COSMIN jointly released the guidelines for selecting the outcome measurement tool for the COS, in order to help researchers choose the right measurement tool for each outcome after completing the COS. The release of these statements and guidelines is a milestone in the study of COS and provides favorable methodological support.

The concept of COS has been introduced into the field of traditional Chinese medicine clinical trials since 2013 by Chinese researchers [10,11], then Chinese medicine researchers began to pay attention and register COS in the COMET database, including diseases such as stable angina pectoris, chronic hepatitis B, nonvalvular atrial fibrillation, non-small cell lung cancer, hyperlipidemia and so on [12-16]. Currently there are more than 1,000 studies in the COMET database, but the methods used in these studies and the handling of details are not uniform, and the quality of research is not clear. Therefore, the work group of COMET released the COMET Handbook (version 1.0) in June 2017, which comprehensively discussed the status and problems in the production, implementation, review and update of COS, and put forward their suggestions [17]. This paper interprets the key points of the COMET Handbook (version 1.0) and discusses its insight on the construction of traditional Chinese medicine clinical trials COS,

combined with the characteristics of traditional Chinese medicine clinical trials, in order to provide a reference for related researchers.

1 Interpretation of the key points of the "COMET Handbook"

At present, most of the studies of COS applied one or more methods of systematic review, nominal group method, Delphi survey, consensus conference and semi-structured interview, but there is no conclusion about which method is the "gold standard" for developing COS. The "COMET Handbook" discusses the pros and cons of these methods and presents the flow chart of developing COS (Figure 1).

1.1 The method of making COS

The "COMET Handbook" puts forward four steps to develop COS, discusses the details of each step that may affect the result of the research, and gives recommendations on some issues as follows:

1.1.1 Confirm the scope of COS

The first step is to confirm the scope of COS (including the target disease, the target population, interventions). Researchers should describe the scope of COS: applicable to all or part of the population of a specific disease (such as all breast cancer patients, or only for patients with metastatic breast cancer); for all types of interventions or specific intervention types (such as surgery, chemotherapy); for effectiveness studies, efficacy studies or clinical practice.

1.1.2 Establishing the need for a COS

The second step is to establish the need to develop a COS. At the beginning, a comprehensive literature search is needed to determine whether there is relevant research. If there is no relevant research, the current clinical studies or systematic review of the outcome's diversity can be assessed, such as the use of an outcome matrix to show the inconsistency and potential reporting bias of outcomes [18]. If there is a clear need to develop a COS, and there is an existing relevant COS, you should carefully consider whether it is necessary to create a new COS. A new COS may still be needed if the existing COS was developed with fewer stakeholders, or the scope of the consensus is limited, or the methodology is not complete. If other work groups are conducting similar research, consider whether they can collaborate to improve the relevant research and avoid duplication.

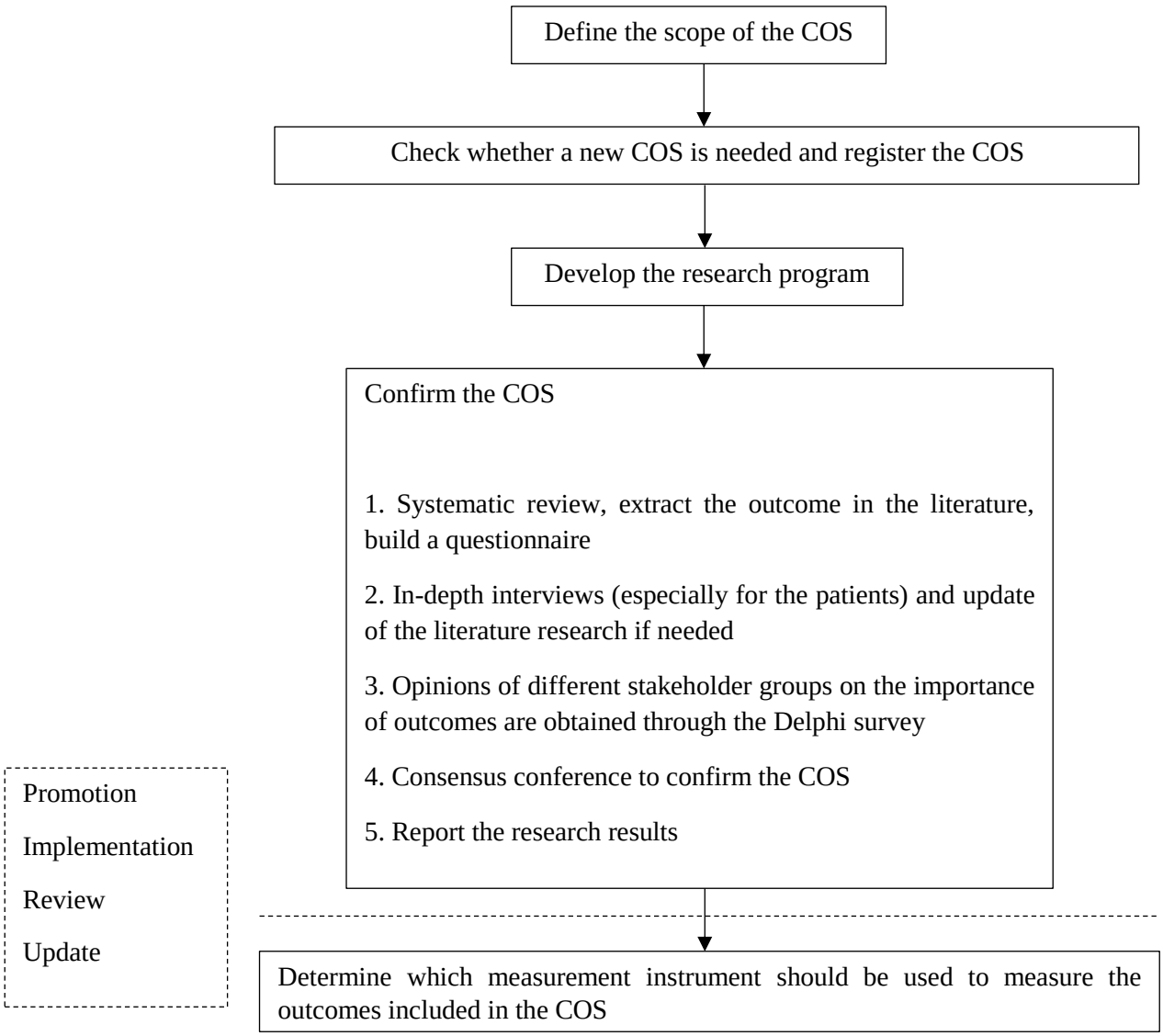

Figure 1 the flow chart of making COS

1.1.3 Develop research program

The third step is to develop a research program. In the protocol, investigators should identify the relevant stakeholders (such as doctors, researchers, patients, policymakers, industry representatives and the public) involved in the research of COS. The number of participants, their representation, their ability to participate and potential conflicts of interest should be taken into account, in different groups, when choosing stakeholder groups. In general, at least health professionals and patients should be involved in the study.

1.1.4 Confirm the outcomes that the COS should measure

The fourth step is to confirm the outcomes of the COS that should be included. There are six main steps:

1) Build the original list of outcomes through a systematic evaluation. In systematic reviews, the search timeframe should be as short as possible (eg, within 24 months) to avoid excessive workload and to help researchers obtain the latest outcomes.

2) Qualitative research, such as semi-structured interviews with patients. Obtain the patient's understanding of the importance of outcomes, supplementing the original list of outcomes.

3) Outcomes can be categorized and divided into 12 categories: mortality, physiological (or pathophysiological) indicators, infection, pain, quality of life, mental health, psychosocial indicators, function (or functional status), treatment compliance, resource utilization (or utilization of medical resources), adverse events (or side effects) and other.

4) Determine the list of outcomes in the questionnaire. The questionnaire should ensure that the structure is clear, the content is comprehensive, and language is concise.

5) Short-term or long-term outcome measures; need to consider the measurement time. For example, a COS recommends assessing radiation damage only in studies that have been followed for more than a year [19].

6) Determine the importance of outcomes. The importance of outcomes is the key to determining whether it can be incorporated into COS. Most studies use a 9-point Likert scoring system, which states that 1 to 3 represent “unimportant” outcome, 4 to 6 for “important” and 7 to 9 for “very important”. An outcome can be incorporated into COS if this outcome of 7 to 9 points occupies more than 70%.

However, there are many factors that may influence the judgment of different stakeholders on the importance of outcomes and even the final outcomes in a COS. In this regard, the “COMET Handbook” discusses the related factors in detail and recommends solutions (Table 2).

1.2 Choose a suitable measurement tool for each outcome

The aim of making a COS is to help clinicians or systematic reviewers choose the outcomes that should be measured in order to increase research value. Therefore, after completing the COS, the investigators should also choose a suitable measurement tool for each outcome in the COS, avoiding the inability to merge due to the diversity of measurement tools.

1.3 The promotion method of COS

Researchers should promote this complicated COS in a variety of ways and encourage more

researchers to use it. At the same time, they can also cooperate with journals, funding sponsors and clinical trial registration centers to urge these institutions to examine whether the COS has been used in research publications, funding applications and research program registrations so as to promote the use of the COS. This implementation is also more conducive to the discovery of potential selective reporting bias in research publication.

1.4 The updating method of COS

There is no "gold standard" for the method of making COS, but the quality of different methods and their impact on the results are not yet completely clear and need further study. As research continues to be added and updated, COS should also be regularly reviewed and updated (eg, every five or ten years) to assure practicality and relevancy.

2 The insight of the "COMET Handbook" on the construction of traditional Chinese medicine clinical trials COS

The concept of COS was originally proposed by some western scholars for the inconsistent reporting of outcome indicators in clinical trials and systematic reviews and belongs to the emerging field of research. The concept of COS has been introduced into traditional Chinese medicine clinical trials for less than 5 years, and only a few researchers are concerned about it. The "COMET Handbook" provides a good methodological reference for COS researchers. However, researchers cannot copy the "COMET Handbook" to make COS related to traditional Chinese medicine clinical trials because of the differences in the theoretical system of traditional Chinese medicine and western medicine, and problems specific to traditional Chinese medicine research. Therefore, the authors offer analysis and insight on the construction of traditional Chinese medicine clinical trials COS according to the content of "COMET Handbook", to provide a reference for related researchers.

2.1 Emphasizing the necessity of establishing COS in traditional Chinese medicine clinical trials

The "COMET Handbook" states clearly that the need to develop a COS should be clarified prior to conducting the study. For example, the authors intend to develop a COS for the treatment of atrial fibrillation in traditional Chinese medicine., They found three related studies in the COMET database, only one study reached a consensus in the area of death, stroke, symptoms and quality of life, rhythm, left ventricular function, cost of treatment, emerging outcome measures (eg, clotting factor, inflammatory mediators, histology and molecular markers) in the way of consensus conference which was initiated by the German Atrial Fibrillation and the European Association of Cardiac Arrhythmias in 2007 [20]. This study only used the method of consensus conference and it is not clear whether the findings are influenced

by individual experts. However, the use of this study is not optimistic according to the systematic reviews published in recent years: 1) there is still confusion about whether the COS is suitable for short term follow-up; 2) there has been no review and update, the latest outcome measures have not been taken into account; 3) only clinical experts, industry representatives and researchers were involved in the stakeholder groups, so there is a lack of patients' opinion. Therefore, this research needs to be further improved in methodology.

Traditional Chinese medicine clinical studies and systematic reviews of atrial fibrillation showed that the outcome selected by Chinese medicine researchers are mainly based on clinical efficacy, symptoms, electrocardiogram efficacy, traditional Chinese medicine syndromes and other alternative indicators, important outcomes such as stroke or mortality were seldom reported, and this is very different from research abroad [21]. Therefore, it is not entirely suitable to use the existing COS in traditional Chinese medicine clinical research. A COS suitable for clinical trials of traditional Chinese medicine should at least have the involvement of Chinese medical researchers. Whether traditional Chinese medicine syndromes should be included in COS should be the consensus among traditional Chinese medicine clinicians and traditional Chinese medicine clinical researchers. It is necessary to reach a consensus at least among Chinese medical clinicians and Chinese medical researchers about whether the common traditional Chinese medicine syndrome efficacy outcomes should be included in the clinical research of traditional Chinese medicine. In order to ensure the feasibility and promotion of COS, patients should be involved in the study. COS should be constructed on the basis of systematic evaluation according to the best evidence principles advocated by the evidence-based medicine model. In summary, the authors contacted the COMET work group to register a COS for clinical research of atrial fibrillation and set its scope of application as non-valvular atrial fibrillation with the addition of traditional Chinese medicine treatment. It has been approved by the COMET working group and has been included in the COMET database.

2.2 Focus on outcomes related to the syndrome

The contemporary clinical treatment modes of traditional Chinese medicine are syndrome differentiation and treatment in traditional Chinese medicine, the combination of disease differentiation in traditional Chinese medicine and treatment based on syndrome differentiation, syndrome differentiation in traditional Chinese medicine but application with specific traditional Chinese medical prescriptions and medications, disease diagnosis based on western medicine but treatment based on traditional Chinese medicine syndrome differentiation, disease diagnosis based on western medicine but treatment with specific traditional Chinese medical prescriptions and medications, treatment based on syndrome differentiation when no disease

diagnosis, treatment based on disease when no syndromes and so on. The most commonly used is the pattern of disease diagnosis based on western medicine but treatment based on traditional Chinese medicine syndrome differentiation [22]. In these modes, traditional Chinese medicine syndrome differentiation is very important. At present, most of the traditional Chinese medicine clinical trials report the symptoms of syndrome. Therefore, when developing a COS, the indicators related to the syndromes should be included in the original list of outcomes at least.

It was suggested that COS should be considered in traditional Chinese medicine clinical trials when COS was introduced into this field [10]. In addition, the State Food and Drug Administration pointed out that clinical trials of traditional Chinese medicine should observe the syndromes and curative effect of Chinese Medicine in the "General Principles of New Drug Clinical Research" and "Chinese Medicine Registration Supplementary Provisions" [23,24]. In recent years, more and more attention has been paid to the study on new drugs of traditional Chinese medicine syndrome. Therefore, we can consider constructing the COS of traditional Chinese medicine syndromes to evaluate the curative effect of syndromes [25] for this kind of research.

2.3 Literature research should be comprehensive

In the current clinical practice and research of traditional Chinese medicine, western medicine still dominates and the treatment methods (such as traditional Chinese medicine, massage and acupuncture) are often used as an adjunctive therapy. Currently, it is very difficult for most diseases to be ethically reviewed when there is only Chinese medicine intervention and without any western conventional treatment, unless there is no valid treatment, or if there is sufficient evidence that discontinuation of conventional western medicine will not cause harm to the patient. Coupled with the current general low quality of clinical research in Chinese medicine, most of the traditional Chinese medicine research only report the intermediate alternative indicators, only a small number of Chinese medicine research reports end points [26,27]. Therefore, in order to ensure the comprehensiveness of the initial outcome checklist, researchers should search for Western-related research, when doing a systematic review, to avoid missing important outcomes.

2.4 The selection of stakeholder groups should be comprehensive

In the process of consensus, the stakeholders should be selected comprehensively to make sure there is broad representation when the COS is eventually formed. The "COMET Handbook" suggests that at least health professionals and patients should be involved in the process of developing COS. However, clinical practice and clinical research in traditional Chinese

medicine generally combine western interventions. Therefore, relevant experts (such as clinicians and clinical researchers) in the field of western medicine should be involved in the production of COS in clinical trials of Chinese medicine as one of the stakeholders.

Some experts of western medicine find it difficult to understand Chinese medical theory and even difficult to accept traditional Chinese medicine because of different knowledge systems. Therefore, it is important to understand the preferences and values of Western medicine experts in advance and to select experts who are interested in the research of Chinese medicine to reduce the chance of missing outcomes or it being difficult to reach a consensus due to the misunderstanding of traditional Chinese medicine. In addition, the experts who are in the field of integrated traditional Chinese and western medicine are more neutral and objective about the understanding of Chinese and Western medicine and can participate in the study as one of the stakeholder groups.

The number of experts in the fields of Chinese and Western medicine should be balanced in the production of COS in clinical research of Chinese medicine, although the "COMET Handbook" points out that there should be as many expert representatives as possible for each stakeholder group. It may lead to some important outcomes not being included in the COS if Western medicine experts are too few and their views are then easily overlooked; excessive number of Western medicine experts may cause difficulties for the consensus or lead to the final COS tending to Western medicine research and a lack of traditional Chinese medicine outcomes. During the Delphi investigation, it is not advisable to conduct a survey of Western medicine experts on indicators related to Chinese medicine so as to avoid making unreasonable judgments due to the differences in knowledge structure and affecting the final result of COS.

2.5 Patients should be representative as one of the stakeholder groups

In the practice of traditional Chinese medicine clinical practice, "the combination of four diagnostic methods" (such as inspection, auscultation and olfaction, inquiry, pulse-taking and palpation) has always been throughout the diagnosis and treatment, doctors and patients will have close communication, and the patient's participation is generally high. Patients should be involved as a stakeholder group in the process of developing COS clinical research. The representation of patients should be fully taken into account when selecting patients, especially their education and social status. The difference of educational backgrounds may affect patients' understanding of the research and may also affect social status or subjective feelings of social status to a certain extent, ultimately affecting the result of the COS. Previous studies have

shown that the worse the individual's subjective perception of social status and the worse his physical condition, the subjective feelings of social status may affect different patients' understanding of the importance of outcomes [28,29]. At present, there are some differences in the distribution of diseases among urban residents and rural residents in our country. The pressures they face are different, their health conditions and their expectations of health are different. Even under the tremendous pressure of life and work, the real social status and subjective social status is not consistent. If the selected patient population is too single, the patient's understanding of the importance of outcomes may not represent all the affected population, affecting the composition of the final COS.

2.6 Emphasis on the measurement time of outcome

At present, the outcome of clinical trials in traditional Chinese medicine is mainly based on intermediate substitution indices and seldom reports on endpoint indices. Therefore, many systematic reviews conclude it is difficult to judge the long-term efficacy of Chinese medicine. The reason is related to the short follow-up time of most traditional Chinese medicine clinical trials, but it does not rule out the possibility of selective reports. In our opinion, the predominant diseases treated by traditional Chinese medicine are mainly chronic diseases. Different studies have different purposes and the length of observation time is also different. It is not appropriate to blindly pursue the end point of the report. Therefore, the COS should be clear in each outcome of the measurement of the time point, so that Chinese medicine COS can be suitable for different times of follow-up in studies.

3. Insight

There are many benefits to developing COS and applying them to clinical trials. 1) addresses the heterogeneity of reporting clinical outcomes of similar clinical trials so that more studies can be included in a systematic review / meta-analysis to provide a higher level of evidence for clinical practice [4]; 2) standardize the indicators that must be reported in similar clinical trials to help systematic review researchers more easily identify selective reporting bias in studies [2,30,31]; 3) report important outcomes that can increase the value of clinical trials and reduce the waste of research funding [32]. If researchers choose unreasonable outcomes and outcome measurement instruments, they may be contrary to ethics, because patients take the risk of participating in clinical research, but their contribution to the whole knowledge system is less or no contribution due to low quality or low value [33]. Therefore, to standardize the set of important outcome measures that should be reported in clinical trials can improve the quality and value of the research so that the findings can guide clinical decision-making [34].

At present, many COS-related researchers around the world are enough to arouse the attention of the COMET working group and introduce the “COMET Handbook” to provide guidance and advice to current researchers. There is no “gold standard” for the method of developing a COS, and the current methodology is not perfect. Many problems are not clear yet and further research is needed. However, the publication of the “COMET Handbook” standardizes the current research and improves the quality of COS research undoubtedly.

Clinical research of Chinese medicine requires COS with Chinese characteristics to provide reference for clinical trials of traditional Chinese medicine to select the outcome, to change the phenomenon that subjective outcomes such as intermediate substitution outcomes or quality of life and symptoms are often reported in clinical studies of traditional Chinese medicine, so that clinical trials of traditional Chinese medicine can be more objectified and standardized. Researchers should have sufficiently searched the literature before proposing a COS study. The target disease should be treated with the addition of traditional Chinese medicine treatment; the scope of the disease should not be too broad, so as to avoid considering the commonality of the disease and ignoring unique factors, leading to some key outcomes not being included in the COS. A preliminary literature study should be conducted to analyze the differences in reporting results of different study outcomes and to clearly establish the need for a COS in clinical research of Chinese medicine after the target disease is determined. Researchers need to search the COMET database for any relevant COS studies. If you have completed the study, you need to know whether the study is the latest study, covering all relevant stakeholders and whether the methodology is complete. If the methodology of the study is incomplete or not entirely suitable for the clinical trials of traditional Chinese medicine, you can still try to apply for a new study from the COMET Working Group. The researcher needs to submit a simple research plan which can be submitted only after the approval of the COMET working group.

The development of clinical research COS need to retain the characteristics of traditional Chinese medicine and consider traditional Chinese medicine syndromes. It should reach a consensus among Chinese medicine clinicians and Chinese clinical researchers on whether traditional Chinese medicine syndrome can be included in the final COS. At present, most of the clinical trials of traditional Chinese medicine is the combination of disease diagnosis based on western medicine but treatment based on traditional Chinese medicine syndrome differentiation, of which traditional Chinese medicine syndrome is one of the included criteria for patients and one of the outcomes of efficacy evaluation. Therefore, the authors believe that regardless of whether traditional Chinese medicine syndromes can be incorporated into COS

eventually, it is impossible to evade the syndrome-related outcomes, you should at least be clear of the target disease's conmmon syndrome of traditional Chinese medicine, in order to make COS users be consistent in the choice of syndromes. At present, clinical symptom scores are often used to evaluate the efficacy of syndromes in clinical trials of traditional Chinese medicine. Therefore, to clarify the core symptoms of common syndromes of related diseases can reduce the heterogeneity of efficacy evaluation of traditional Chinese medicine syndromes and help to compare or merge the efficacy of traditional Chinese medicine syndromes.

The introduction of the "Law of the People's Republic of China on Traditional Chinese Medicine" will raise the level of safeguarding and promoting the development of traditional Chinese medicine to a national strategic level. Clinical efficacy is the key to maintain the vitality of the development of Chinese medicine. The clinical efficacy evaluation needs to be consistent with evidence-based medical standards of high-quality evidence, the selection of appropriate and important outcome indicators is the basis. Making COS does not mean that clinicians can not choose other outcomes, but rather that they require that at least COS be reported in all clinical studies. Through the interpretation of the "COMET Handbook", this article hopes that more traditional Chinese medicine researchers focus on COS research, and looks forward to the relevant researchers improving the methodology and promoting the application of COS in research. In the future, more clinical researchers can select well documented outcome indicators and report core outcomes completely to improve the quality and value of clinical research in traditional Chinese medicine. Finally, more studies can be included in systematic reviews and provide a higher level of evidence for clinical practice. In summary, the development of COS will promote the development of evidence-based traditional Chinese medicine research and contribute to the standardization and internationalization of traditional Chinese medicine.

Table 1 Examples of outcome matrix [18]

Reports	Main outcome	Another outcome		Additional outcome*	
	Neonatal live birth rate	Biochemical pregnancy rate	Clinical pregnancy rate	Ectopic pregnancy rate	Neonatal weight

Smith 1999	0	X	√	X	X
Lowe 2001	√	0	X	√	X
Biggs 2004	X	√	√	X	√

*: outcome of any research report; √: The full report of the corresponding outcome; X: The corresponding outcome is not reported; 0: Outcomes reported incomplete

Table 2 Associated determinants with COS and suggestions for resolution

Determinants	Problems	Status	suggestions
Number of expert groups	A group of experts does not reflect differences in perspectives among different stakeholder groups; multiple panel groups make it difficult to synthesize the opinions of different stakeholder groups	Different researchers choose different numbers of expert groups	No recommendations
Number of	Too few people will easily result	The number of professional	1) Expert steering committees

participants	in inaccurate results	and technical personnel vary from 12 to 174, the number of patients range from 32 to 185	should be consulted, and the number of participants should be determined based on the actual situation; 2) the representation of experts and their level of understanding of the relevant issues should be taken into account; 3) the more experts per stakeholder group, the better.
Description of questionnaire	Poor or difficult language can affect participants' understanding of research	Unknown	The questionnaire should use easy-to-understand language and expressions to ensure that it is understandable to different stakeholders.
Round of the Delphi survey	Unknown	There are 2 to 3 rounds for general survey, individual research includes up to 6 rounds.	At least 2 rounds should be performed, time, cost and participants' burden should be taken into account; Each round of investigation should last for 2 to 3 weeks, if the response rate is too low, the subsequent investigation may be appropriate to extend the time.
The structure of the questionnaire	Unknown	Unknown	Avoid using terminology, stakeholders should be involved in the design and pre-investigation of the questionnaire to ensure that the questionnaire is understandable and effective.
The order of items in the questionnaire	Affect the response rate; affect the true reflection of participants on each issue	Previous studies showed the response rate and true reflection of participants varied from the order of items.	No recommendations
Open question	List of outcomes that can be enriched and refined	Some studies include open questions, different research purposes have different ways	If placed at the beginning of the questionnaire, participants are asked to answer several of the outcome

		of asking questions and different orders.	indicators they think are most important before they are filled out, ensuring there are no omissions; at the end of the questionnaire, participants are allowed to respond to what they consider to be important, suggesting new items/outcomes.
grading system	Unknown	Different researches select different scoring system, the most typical is the GRADE team recommended 9 Likert score system.	No recommendations
Feedback method	Unknown	When there is only one group of experts, the average scores of all the participants' scores on each outcome are fed back and the opinions of different stakeholders are easily ignored; there are three ways to do this When there are multiple expert groups: 1) feedback the average of all participants scoring each outcome metric; 2) only the average of the stakeholder groups to which the participants belong 3) both groups scores are fed back to the participants.	No recommendations
Keep or delete the items	If all items are kept, the participants may be over burdened with too many outcomes, resulting in loss of follow-up. If some items are deleted, later participants can not rate deleted indicators or you	Which method is better is not conclusive at present, it mainly based on the number of original outcome measures.	All of the outcome measures are retained in the second round, giving the participants the opportunity to re-score based on the results of the feedback, but in the subsequent surveys, some of the outcome can be excluded based on the results of the

	might delete indicators that are important to some participants.		previous two rounds.
loss of follow-up bias	If the loss of follow-up rate is too high will cause loss of follow-up bias, the bias will affect the final result.	Most studies suggest that the response rate of each stakeholder group is around 80%. There are two ways to determine whether there is a follow-up bias: 1) Calculate the average score of each item from the questionnaire and the incomplete; 2) calculate the average of the completed and unfinished outcomes.	If the loss of follow-up rate is too high, researchers should adopt some strategies, such as email or telephone reminder, or appropriate extension of the investigation time. Researchers should select the appropriate method to determine whether there is a loss of follow-up bias.
The definition of consensus	It may lead to too many outcomes included in the COS if the consensus criteria are too broad; It may lead to some of important outcomes not being included in the COS if the consensus standards are too strict.	Different studies have different definitions of "consensus" and there is currently no uniform standard	No recommendations. The COS researchers should be clear in the program in order to avoid bias in the standard changes after the Delphi survey is completed.
The level of consensus	Each round of Delphi survey should assess the extent of consensus reached, and determine whether it is necessary to continue the Delphi survey to reach consensus.	Methods to assess the degree of consensus include: 1) comparing the number of participants who changed scores between different rounds, expressed as a percentage; 2) comparing the changes in each of the two rounds of outcomes with a standard deviation or quartile.	No recommendations. The COS researchers should be clear in the program and reported in detail in the study results. Explain why if inconsistent with the research program