

Core outcome set for stable angina pectoris in traditional Chinese medicine (COS-SAP-TCM)

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Abstract

Objective: This study aimed to develop a core outcome set (COS) for use in future studies of stable angina pectoris (SAP) in traditional Chinese medicine (TCM).

Methods: Systematic literature reviews and qualitative interviews with cardiologists and patients with SAP treated using TCM were conducted to generate a set of outcomes. Outcomes were prioritized by stakeholders via two rounds of an online Delphi survey and face-to-face consensus meetings. Following the final consensus meeting, a final COS was generated.

Results: An initial set of 324 outcomes was identified. A preliminary list of 65 outcomes was employed in the Delphi study. In total, 223 participants from seven stakeholder groups were invited to score outcomes in the first Delphi round: 87 completed round 1 and 47 completed round 2. Thirty-one participants attended the consensus meeting and agreed on a final core set of outcomes comprising six items across four domains: frequency of angina attack, duration of angina attack, Seattle angina questionnaire, total exercise duration in the exercise treadmill test, cardiovascular events, and QT interval on electrocardiography.

Conclusions: The COS developed in this study provides the minimum requirements for measurement and reporting in future TCM clinical trials for the treatment of SAP. The employment of this COS may reduce heterogeneity across trials and facilitate evidence-based decision-making for stakeholders.

Keywords: Core outcome set, Outcome measure, Stable angina pectoris, Traditional Chinese medicine

1 Introduction

Stable angina pectoris (SAP) is generally associated with myocardial ischemia or hypoxia and manifests clinically as transient chest discomfort^[1-2]. In most patients, the underlying mechanism is thought to be due to significant obstructive coronary artery disease (>70% narrowing of the diameter of one or more vessels), which limits the increase in coronary blood flow during periods of increased myocardial oxygen demand during exertion^[2-6]. The annual death rate of patients with SAP is 1% to 3%^[4-7]. The use of conventional antianginal drug therapies such as organic nitrates, β -blockers, calcium channel blockers, nicorandil, and ivabradine can effectively control angina and improve exercise tolerance^[8-10]. Nevertheless, there is insufficient evidence for the impact of conventional drug therapies on adverse clinical cardiac outcomes in patients with stable angina. Further, the long-term use of these drugs causes side effects such as headaches and gastrointestinal ulcerations^[8].

In China, there is a growing number of clinical trials using traditional Chinese medicine (TCM) for the treatment of SAP to provide evidence for the efficacy and effectiveness of TCM-based therapies^[11-15]. Syndrome (pattern) differentiation provides the basis for TCM therapeutic principles and is determined using the four methods of diagnosis: tongue examination, history-taking (inquiry), listening and smelling examinations, and palpation (such as pulse-taking and abdominal examination). Syndromes (patterns) also reflect the etiology and nature of diseases at certain stages.

Several studies have reported the effectiveness of TCM for the treatment of SAP, but these results should be treated with caution due to poor methodological quality in clinical trials^[15-16]. A crucial aspect underpinning this poor methodological quality is the heterogeneity in reporting of outcomes^[17]. Several issues regarding the selection and reporting of outcome measures for TCM clinical trials include substantial variation in measured and reported outcomes across clinical trials for the same condition. Further, many studies are underscored by selective reporting bias, lack of reporting on primary and long-term outcomes, and poorly defined or standardized outcomes for TCM-related syndrome changes^[17-18]. Selective reporting of outcomes precludes comparison across trials, thereby limiting the validity of meta-analyses and reducing the value of clinical research. Hence, the selection of appropriate outcomes is crucial when designing clinical trials to ensure reproducibility in research^[19].

A core outcome set (COS) is a standardized set of outcomes that should be measured and reported as a minimum in all trials in the same field of healthcare^[20]. This study aimed to develop a COS for evaluating the effectiveness of TCM-based interventions for the treatment of SAP in order to minimize heterogeneity in reported outcomes and improve the methodological quality of TCM-related clinical research. In this study,

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we report the development of a COS for SAP in TCM (COS-SAP-TCM). The COS was derived from various sources, which formed an outcome pool for the generation of preliminary outcomes to be included in the consensus process. The COS-SAP-TCM developed herein can be used in clinical trials, systematic reviews or meta-analyses, and other evidence-based research on SAP.

2 Methods

2.1 Study overview

The scope of the COS was defined according to the COS-standards for development (COS-STAD)^[21]. The study population comprised adults aged ≥ 18 years with SAP who had received TCM-related interventions, including herbal medicine decoctions, Chinese patent medicines, herbal medicine extracts, Chinese medicine injections, acupuncture, cupping, Tuina (TCM massage), moxibustion, and TCM rehabilitative therapies. This study was conducted and reported with reference to a series of standards developed by the Core Outcome Measures in Effectiveness Trials (COMET) group^[21–23]. The development of a COS for SAP (Figure 1) in TCM-related clinical trials involved four phases:

- (1) forming a steering committee and working group,
- (2) generating a preliminary list of outcomes,
- (3) two rounds of Delphi surveys, and
- (4) consensus meeting to agree on a final COS.

The project was registered on the COMET initiative website (<http://www.comet-initiative.org/studies/details/391>). All participants provided informed consent to participate in the survey. The study was approved by the Ethics Committee of the Evidence-based Medicine Centre, Tianjin University of Traditional Chinese Medicine (TJUTCM-EC20170008).

2.2 Patient and public involvement

Patients or their representatives participated in semi-structured interviews, two rounds of Delphi surveys, and consensus meetings.

2.3 Stakeholder involvement

The quality of the consensus process was ensured through the professional expertise of stakeholders, which were balanced in composition and comprised stakeholders from various regions. Seven groups of stakeholders were invited to participate in the study including clinicians, clinical researchers, policy-makers, clinical pharmacologists, methodologists, professionals in the pharmaceutical enterprise, and patients. Academic researchers were recruited through the China Association of TCM and Chinese Society of Cardiology. Patient representatives were recruited from inpatient and outpatient clinics of TJUTCM-affiliated hospitals.

2.4 Phase 1: steering committee and working group

The steering committee comprised three TCM clinical experts, three methodologists, two clinical researchers, one policy-maker, and one COS developer. The role of the committee was to review and provide guidance at each stage of the study protocol. The working group comprised

20 individuals, including 18 representatives of cardiologists (western and TCM clinicians), methodologists, clinical researchers, policy-makers, COS developers, and two patient representatives. The group was formed to communicate at various stages of the study and to organize meetings on a regular basis. Disagreements about the results at any phase of the study were discussed during the meetings.

2.5 Phase 2: forming a preliminary list of outcomes

Potential outcomes were identified to generate a list of outcomes on SAP with TCM-based treatments via a systematic review and qualitative survey.

2.5.1 Systematic review: literature and clinical trial registry database search

A comprehensive electronic search strategy of eight databases including PubMed, Cochrane Library, Embase, Web of Science (four English databases), CNKI, Wan-Fang, SinoMed, VIP (four Chinese databases); and two clinical trial registry databases, Clinicaltrials.gov and Chinese clinical trials registry (ChiCTR), was performed to retrieve outcomes for the preliminary list. The literature search was performed using discontinuous time intervals of 2005, 2010, 2015, 2016, and 2017. Clinical trials registry databases were searched from study inception to January 2018. Randomized controlled trials (RCTs), clinical controlled trials, and case reports using TCM or combined TCM and western treatments for SAP were included. Clinical trials involving TCM-related therapies such as acupuncture, Tuina, and acupressure were excluded. Only studies with interventions of TCM herbal decoctions, Chinese patent medicine, or intravenous TCM were included. The included studies were screened independently by two authors, and information on outcomes was extracted. A predesigned access file was used to extract data, including design type, intervention, patient information, clinical characteristics, and outcomes. Outcome information included outcome name, measurement method, measurement time-point, and data type. Information was sorted according to similarities, and duplicate outcomes were excluded. Synonymous outcomes were merged. The process was performed independently by two researchers. Discrepancies were resolved by discussion.

2.5.2 Qualitative survey: clinician and patient questionnaire

Comprehensive inclusion in the preliminary list included a representative mix of outcomes from major stakeholders. Questionnaires were administered across four different hospitals of different grades in Tianjin and Henan (China) to collect outcomes that were of importance to clinicians and patients. The survey period was from 1 September 2017 to 30 November 2017. Cardiologists and patients diagnosed with SAP or their caregivers were surveyed. Clinicians were provided open-ended questionnaires, whereas patients received semi-structured interviews and provided guidance on completing the questionnaire. Examples of guided questions in semi-structured interviews for patients are as follows:

- (1) "In the treatment process of SAP, what type of treatment effect is of utmost importance to you?"
- (2) "With regards to your SAP management, symptoms, or daily life, what kind of changes are most important to help you determine the treatment effect?"

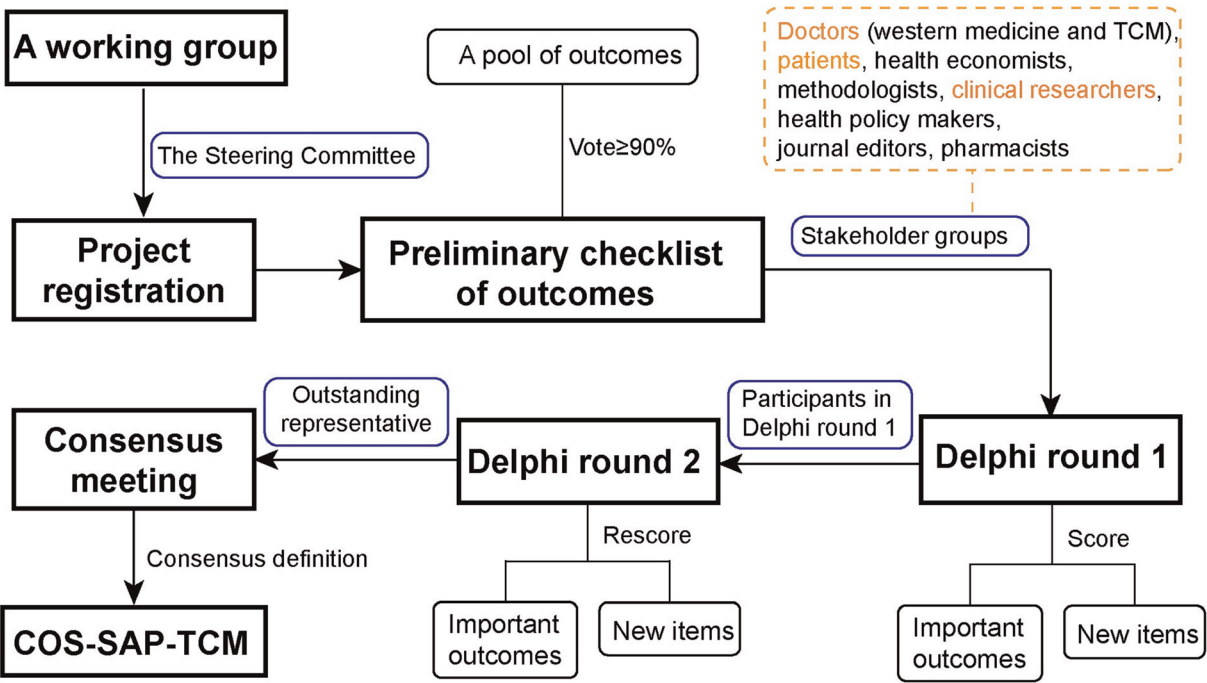


Figure 1. Flowchart of the study.

- (3) “What do you worry about the most for the treatment of SAP, and what aspects do you hope to improve?”
- (4) “Regarding the treatment for SAP, which changes make you feel your condition is improving?”

TCM syndrome classification of patients across different regions in China was included in the survey to identify relationships between TCM syndromes and TCM-related outcomes. An outcome pool consisting of outcomes from the questionnaires, literature, and clinical trial registry databases was formed. Outcomes were then categorized according to their characteristics (primary, secondary outcomes, or endpoints) into seven domains/groups, which included symptoms and signs, physical and chemical indexes, quality of life, TCM-related outcomes, long-term prognosis, economic evaluation, and safety indexes. Some of the items were removed from the list when 90% of the members of the steering committee and working group voted for their unimportance. Finally, the retained outcomes formed the preliminary list for the consensus process.

2.6 Phase 3: Delphi survey

A consensus study was performed using a Delphi process. The Delphi process consisted of two rounds of electronic surveys, with analysis and feedback between rounds. An online survey platform (<https://www.wenjuan.com>) was used to administer the Delphi survey. An e-mail outlining the project and survey as well as a link to the survey questions were sent to all participants (excluding the patient representative group) and a two-week deadline was set for completion of the first round of the Delphi survey. A reminder e-mail was sent to all participants after one week. Patient representatives completed the first round survey via a face-to-face interview with researchers from the working group during consultation under the supervision of outpatient doctors. In round 1, participants scored all outcomes from the preliminary list and added outcomes that were deemed important but were not in

the preliminary list. Additional outcomes added in round 1 were reviewed by the working group to identify and remove duplicates.

Delphi outcome scoring method: A Likert scale with nine scores was used to evaluate the importance of the outcomes. Each outcome was scored from 1 to 9 (unimportant: 1–3; important but not critical: 4–6; critical: 7–9). Participants were able to select “unable to score” if they were undecided about the importance of an outcome. This scoring system was recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group to assess the level of importance of research evidence.

Data from different stakeholder groups in round 1 were compiled and analyzed. Outcomes of >70% of the participants who scored 4–9 in at least one stakeholder group were retained, and the working group discussed the remaining outcomes that were to be retained or removed for Delphi round 2. In round 2, the summarized results for each stakeholder group were provided to all participants who fully completed the survey in the first round. Feedback from round 1 was provided to allow participants to take into account the scores of other participants prior to re-scoring. Each participant was also presented with their score for each outcome in round 1 to provide justification if the participant rescored an outcome from “not critical” (<7) to “critical” (>7) or vice versa. Data from round 2 were analyzed in consideration of scoring distribution, assessment of reason for rescoring, and attrition bias. Outcomes were ranked according to the importance ratings. Outcomes for which consensus was achieved (>70% of the participants scored 7–9 in at least one stakeholder group) (Table 1) were included in the candidate list of core outcomes for the consensus meeting.

2.7 Phase 4: consensus meeting

All outstanding representatives of different stakeholder groups and clinicians who completed the Delphi survey

Table 1**Consensus definition.**

Consensus classification	Description	Definition
Consensus in	Consensus that outcome should be included in COS	>70% score 7–9 in at least one stakeholder group
Consensus out	Consensus that outcome should not be included in the COS	>70% score 1–3 in all participants
No consensus	Uncertainty about importance of the outcome	Anything else

and members of the steering and working groups attended a face-to-face consensus meeting. The meeting process included a brief review of the COS study and a summary of the scoring results of all outcomes from each stakeholder group. Each item in the candidate list of core outcomes was introduced, and the number of stakeholder groups that achieved consensus was noted. Participants voted anonymously for every item on the candidate list of core outcomes. Similar to the survey, each outcome was considered to reach consensus if 70% of participants voted in favor of its inclusion. The voting results were discussed, and a consensus was reached to determine COS-SAP-TCM. All participants had the right to discuss any item. Disputes were settled via a nominal group. Relevant suggestions were provided for subsequent revision and promotion of COS-SAP-TCM.

3 Results

The quality of the consensus process was ensured by the professional expertise of stakeholders and a balanced composition of representatives. This study invited 223 representatives from different stakeholder groups, comprising 105 clinicians, 44 policy makers, 29 clinical researchers, 26 clinical pharmacologists, four methodologists, five professionals from the pharmaceutical enterprise, and 10 patient representatives, to join the Delphi survey.

3.1 Steering committee and working group

The steering committee was composed of three TCM clinical experts, three methodologists, two clinical researchers, one policy-maker, and one COS developer. The committee reviewed and provided guidance at each stage of the study protocol.

3.2 Outcome identification: pool of outcomes

12,939 studies were identified from the literature databases, and 999 studies were included after screening and application of the inclusion and exclusion criteria, which included 350 RCTs, 457 clinical controlled trials, and 192 case reports; 219 outcomes retrieved for SAP. For clinical trial registry databases, 23 clinical trials were included (16 from the ChiCTR and 7 from the Clinicaltrials.gov), with 64 outcomes retrieved. In total, 1,022 studies were identified, including 231 outcomes.

A total of 321 questionnaires were completed (patients: 238; doctors: 83), which included a collection of 80 outcomes from clinician and 69 from patient questionnaires. An outcome pool was formed after outcomes were retrieved and collected from the above sources that were combined and standardized. In total, 324 outcomes were obtained and classified into seven different domains according to their characteristics.

To improve the efficiency and quality of the Delphi survey, the steering committee and working group voted on and discussed the 324 outcomes to be retained or eliminated. A preliminary list of outcomes was formed, which comprised 65 outcomes classified under eight outcome groups. Details are provided in Table 2.

3.3 Delphi survey

In total, 223 participants were invited to vote in the first round of the Delphi survey. A total of 87 participants completed the survey, comprising 28 researchers, 41 clinicians, 8 policy makers, 5 patient representatives, 4 pharmacologists, and 1 methodologist. The attrition rate for round 1 was 60.98% (136/223). After completion of the survey in round 1, four additional outcomes were proposed by three participants: “nature of chest pain”, “blood glucose”, “hypersensitive-C reactive protein (hs-CRP)”, and “low-density lipid (LDL)”. The first three were regarded as new outcomes, whereas “LDL” was regarded as a subgroup classified under “blood lipids.” Two participants highlighted that “LDL” was considered an important outcome by many clinicians, hence, all four of the aforementioned outcomes were retained and included in Delphi round 2. Scores for each outcome and score distributions for each stakeholder group were analyzed. Outcomes were ranked according to their importance (proportion of participants with score ≥ 4 for the outcome) (Table 3). In total, 41 outcomes were regarded as “important” based on statistical evidence, which were retained for Delphi round 2. The remaining 24 outcomes were discussed in relation to their average scores and research feasibility. Of the 24 remaining outcomes, four (consultation frequency, blood pressure, ejection fraction, and tongue and pulse examination outcomes) did not reach a consensus to be removed. A decision was made by the steering committee to retain these outcomes. A final total of 49 outcomes was included in Delphi round 2.

In round 2, 47 participants completed the survey, with an attrition rate of 45.98% (40/87) from round 1. Scores of the 49 outcomes were tallied and ranked according to whether they were regarded as “critical” (Table 4). With reference to the consensus definition, 29 outcomes that were determined as “consensus in” (outcomes designated a score of 7–9 by at least one stakeholder group) formed the candidate list of core outcomes for the consensus meeting (Table 5).

3.4 Consensus meeting

The consensus meeting involved a 1-day face-to-face meeting held in Tianjin, China on 28 January 2018. The meeting involved 31 participants comprising 8 clinical researchers, 10 clinicians, 4 methodologists, 2 patient representatives, 3 policy-makers, 2 journal editors, and 2 pharmaceutical enterprise representatives. No conflict of

Table 2
Preliminary list of outcomes for Delphi round 1.

Outcome domains (subgroup)	Outcome
Clinical symptoms and signs (12)	Chest tightness
	Fatigue
	Palpitation
	Angina occurrence situation: degree of angina pain
	Angina occurrence situation: frequency of angina occurrence
	Angina occurrence situation: angina duration
	Nitroglycerin dosage
	Symptom score
	Comfortable sensation experienced by self
	Seattle angina scale
	NYHA grading
	Blood pressure
TCM-related outcomes (5)	TCM syndrome score
	TCM symptom score
	TCM single symptom score
	Tongue and pulse
	Sleep quality
Electrocardiography (ECG) outcomes (5)	ST segment depression
	Low or inverted T wave leads
	Total load of dynamic electrocardiogram myocardial ischemia
	Arrhythmia
	Heart rate variability
Treadmill test-related outcomes (4)	Treadmill test duration
	Duke score
	ST segment depression 1-mm duration
6-minute walk test (6MWT)-related outcomes (2)	ST segment depression 1-mm lead
	6MWT distance
Prognosis-related outcomes (11)	Myocardial oxygen consumption
	Mortality rate
	Duration of survival
	Consultation frequency
	Rehospitalization rate
	Cardiovascular events
	Heart failure
	Myocardial infarction
	Apoplexy
	Sudden cardiac death
	Unstable angina pectoris
	Stent-free rate
Psychological health-related outcomes (2)	Psychologic rating scale
	Mental status
Physical and chemical examinations (24)	Coronary artery organic stenosis
	Arterial stiffness
	Carotid arterial intima-media thickness
	Maximum velocity of carotid artery ultrasound
	Blood lipids
	Hemorheology index
	Brain natriuretic peptide
	Left ventricular ejection fraction
	Vascular endothelial growth factor
	C-reactive protein
	Hypersensitive C-reactive protein
	Endothelin
	Cystatin C
	Tumor necrosis factor TNF- α
	Superoxide dismutase
	Visfatin
	Thromboxane
	Platelet aggregation rate
	Nitric oxide synthase
	Nitric oxide
	Homocysteine
	Neurotransmitter
	Four blood coagulation indexes
	Inflammatory factors

AE: Adverse events; AECG: Active electrocardiography; AP: Angina pectoris; APTT: Activated partial thromboplastin time; BAPWV: Brachial-ankle pulse wave velocity; BNP: Brain natriuretic peptide; CSS: Clinical symptoms and signs; CTA: CT angiography; ECG: Electrocardiogram; EE: Economic evaluation; EF: Ejection fraction; ET-1: Endothelin-1; ETT: Exercise treadmill test; FIB: Fibrinogen; Hcy: Homocysteine; HRV: Heart rate variability; IMT: Intima-media thickness; LTP: Long-term prognosis; METs: Metabolic equivalents; NO: Nitric oxide; NOS: Nitric oxide synthase; PCE: Physical and chemical examination; PT: Prothrombintime; QL: Quality of life; SAQ: Seattle angina questionnaire; SOD: superoxide dismutase; TCMO: TCM-related outcomes; TIB: Total ischemia burden; TXA2: Thromboxane A2; TXB2: Thromboxane B2; TT: Thrombin time; VEGF: Vascular endothelial growth factor; Vmax: Maximum blood flow velocity; 6MWT: 6-minute walking test.

interest among the different stakeholders was noted. Before discussion among the stakeholders, the scores of each outcome from the two rounds of the Delphi survey were presented to all participants. In total, 27 participants voted anonymously for the 29 outcomes in the candidate list via consensus. After voting, seven outcomes which met the consensus criteria were retained as the final core outcomes (>70% of the votes), consisting of frequency of angina, angina duration, treadmill test duration, cardiovascular events, and subdomain outcomes of myocardial infarction, unstable angina pectoris, and sudden cardiac death (Table 6). Discussion for the final COS was conducted. This included outcomes in the candidate list of core outcomes for which consensus was not reached and additional outcomes which the steering committee deemed to be of importance. “Seattle angina scale” (from the 29 outcomes of the candidate list) and “QT interval” were proposed for inclusion in the final COS. TCM-related outcomes were not highly regarded as important outcomes during the consensus process. The steering committee decided to add relevant TCM-related outcomes for COS-SAP-TCM to strengthen the development and evidence-based nature of TCM clinical studies in the future. The final COS-SAP-TCM consisted of frequency of angina occurrence, angina duration, Seattle angina scale, treadmill test duration, myocardial infarction, unstable angina pectoris, sudden cardiac death and QT interval (Figure 2).

4 Discussion

A COS is a minimum set of outcome measures that are agreed upon and standardized for use in a specific healthcare area. Researchers can design their studies based on a COS and can add or remove outcomes relevant to their study design according to intervention-responsiveness and feasibility. Developing a COS is critical to reduce heterogeneity of outcomes across studies and to enable a comparison of results for evaluation of interventions and ensuring the benefits of therapies or health policies.

This study aimed to develop a COS for TCM in order to encapsulate the unique characteristics of TCM, including symptoms and clinical remission, and to gain recognition on an international level. In this study, an insignificant number of TCM-related outcomes was included in the Delphi survey, and only “TCM symptom score” was included in the consensus meeting. The lack of TCM-related outcomes in COS-SAP-TCM affects the reflection of crucial TCM characteristics. This could be due to the complex nature of TCM mechanisms, difficulty in obtaining direct evidence, and selection of outcomes commonly used in modern medicine in TCM clinical trials. Many stakeholders did not emphasize the inclusion of TCM-related outcomes in the outcome selection process. Indeed, TCM-related outcomes tended to be overlooked in the consensus process, highlighting the need for improvements in the quality of TCM outcome measures. Another potential reason is that TCM-related symptom outcomes, despite having different names, might have overlapped with common symptom outcome measures, affecting the proportion of TCM-related outcomes included in the selection process.

The Delphi and consensus process methods have been used extensively in the development of COSs. In the Delphi process, the degree of consensus for outcomes

Table 3**Important (≥ 4 points) outcomes in Delphi round 1.**

Ranking	Outcome	Domain	Percentage scoring ≥ 4	Average
1	SAQ	CSS	0.90	6.84
2	Pain degree	CSS	0.89	7.36
3	Myocardial infarction	LTP	0.87	7.36
4	Duration	CSS	0.87	7.23
5	Time to onset of chest pain	ETT	0.87	6.80
6	Attack times	CSS	0.86	7.06
7	Chest distress	CSS	0.86	6.77
8	CTA coronary stenosis	PEC	0.86	6.63
9	Time to 1-mm ST-depression	ETT	0.86	6.62
10	Duke treadmill score	ETT	0.86	6.53
11	Nitroglycerin consumption	CSS	0.86	6.52
12	TIB	ECG/AECG	0.85	6.52
13	Number of leads with ST-depression ≥ 1 mm	ETT	0.85	6.43
14	Arterial stiffness	PEC	0.85	5.82
15	Cardiogenic death	LTP	0.84	7.07
16	Unstable angina pectoris	LTP	0.84	6.98
17	Cardiovascular event	LTP	0.84	6.94
18	Angina symptom score	CSS	0.84	6.00
19	Heart failure	LTP	0.82	6.75
20	All-cause mortality	LTP	0.82	6.70
21	ST segment depression	ECG/AECG	0.80	6.22
22	Blood lipids	PEC	0.80	5.42
23	Flatness or inversion of T wave	ECG/AECG	0.79	6.11
24	Cardiac function grading	CSS	0.79	6.02
25	Myocardial oxygen consumption	6MWT	0.79	5.83
26	Re-hospitalization	LTP	0.78	6.00
27	Walking distance	6MWT	0.78	5.93
28	Stroke	LTP	0.76	6.03
29	Score of TCM symptoms	TCMO	0.76	5.69
30	Carotid IMT	PEC	0.76	5.42
31	Palpitation	CSS	0.76	5.40
32	Survival time	LTP	0.75	6.28
33	Coronary stent implantation	LTP	0.74	5.83
34	Score of TCM single symptom	TCMO	0.74	5.43
35	Mental status	Psychological health	0.74	5.16
36	BNP	PEC	0.74	5.10
37	Score of TCM syndromes	TCMO	0.72	5.43
38	Psychologic rating scale	Psychological health	0.72	5.11
39	Arrhythmia	ECG/AECG	0.71	5.44
40	Carotid ultrasound Vmax	PEC	0.71	5.05
41	HRV	ECG/AECG	0.70	5.22
42	Clinic visits	LTP	0.69	5.02
43	EF	PEC	0.68	5.22
44	Conscious comfort	CSS	0.68	5.13
45	Fatigue	CSS	0.66	4.73
46	CRP	PEC	0.66	4.61
47	Tongue and pulse	TCMO	0.64	5.18
48	Platelet aggregation	PEC	0.64	4.70
49	Blood pressure	CSS	0.63	4.86
50	VEGF	PEC	0.63	4.64
51	hs-CRP	PEC	0.62	4.62
52	NOS	PEC	0.62	4.47
53	Hemorheology indexes	PEC	0.61	4.39
54	Inflammatory factors	PEC	0.61	4.38
55	Four items of coagulation	PEC	0.60	4.39
56	Thromboxane	PEC	0.60	4.28
57	Endothelin	PEC	0.59	4.55
58	Hcy	PEC	0.59	4.27
59	NO	PEC	0.57	4.30
60	Cystatin C	PEC	0.57	4.25
61	The quality of sleep	TCMO	0.54	4.51
62	Visfatin	PEC	0.53	3.95
63	TNF- α	PEC	0.52	3.87
64	SOD	PEC	0.48	3.83
65	Neurotransmitter	PEC	0.48	3.76

Table 4**Critical (7–9 points) outcomes in Delphi round 2.**

Ranking	Outcome	Domain	Health-decision makers	Users	Healthcare professionals	Patients	Percentage scoring 7–9	Average
1	Cardiovascular event	LTP	100%	86%	88%	80%	87%	7.49
2	Chest distress	CSS	100%	79%	85%	100%	85%	7.68
3	Duration	CSS	100%	71%	92%	80%	85%	7.70
4	Myocardial infarction	LTP	100%	71%	92%	80%	85%	7.79
5	Pain degree	CSS	50%	79%	88%	80%	83%	7.45
6	Attack times	CSS	100%	71%	88%	80%	83%	7.60
7	SAQ	CSS	100%	71%	92%	40%	81%	7.38
8	Cardiogenic death	LTP	100%	64%	88%	80%	81%	7.51
9	Unstable angina pectoris	LTP	100%	71%	85%	80%	81%	7.28
10	Nitroglycerin consumption	CSS	100%	79%	77%	80%	79%	7.26
11	Time to onset of chest pain	ETT	50%	71%	85%	80%	79%	7.15
12	CTA coronary stenosis	PEC	0%	86%	81%	80%	79%	7.54
13	Heart failure	LTP	50%	71%	73%	80%	72%	6.94
14	TIB	ECG/AECG	100%	71%	73%	60%	72%	7.11
15	Time to 1-mm ST-depression	ETT	50%	71%	81%	40%	72%	7.02
16	All-cause mortality	LTP	50%	50%	85%	60%	70%	6.93
17	Number of leads with ST-depression ≥ 1 mm	ETT	50%	64%	81%	40%	70%	6.80
18	Duke score	ETT	50%	71%	77%	20%	68%	6.95
19	Survival time	LTP	0%	50%	73%	80%	64%	6.54
20	Walking distance	6MWT	50%	50%	65%	100%	64%	6.47
21	Angina symptom score	CSS	100%	36%	69%	60%	60%	6.70
22	ST segment depression	ECG/AECG	100%	50%	58%	80%	60%	6.67
23	Rehospitalization	LTP	50%	43%	65%	60%	57%	6.45
24	Stroke	LTP	50%	64%	54%	60%	57%	6.35
25	Flatness or inversion of T wave	ECG/AECG o	100%	57%	46%	80%	55%	6.73
26	Myocardial oxygen consumption	6MWT	50%	71%	42%	60%	53%	6.40
27	Characteristics of chest pain	Added outcome	50%	43%	54%	60%	51%	6.27
28	Coronary stent implantation	LTP	50%	57%	38%	80%	49%	6.37
29	Cardiac function grading	CSS	50%	50%	38%	60%	45%	6.19
30	Score of TCM syndrome	TCMO	0%	36%	46%	80%	45%	6.11
31	Score of TCM symptoms	TCMO	50%	43%	38%	80%	45%	6.36
32	Troponin	Added outcome	50%	29%	50%	60%	45%	6.02
33	Arterial stiffness	PEC	0%	43%	38%	80%	43%	6.43
34	Score of TCM single symptom	TCMO	50%	29%	42%	60%	40%	6.00
35	Tongue and pulse	TCMO	0%	7%	54%	60%	38%	5.89
36	Blood lipids	PEC	0%	36%	42%	40%	38%	6.18
37	Clinic visits	LTP	0%	36%	27%	80%	34%	5.58
38	Carotid IMT	PEC	0%	43%	31%	40%	34%	5.91
39	EF	PEC	0%	43%	27%	60%	34%	5.91
40	Palpitation	CSS	50%	33%	23%	80%	32%	5.33
41	LDL	Added outcome	50%	7%	42%	40%	32%	5.78
42	Arrhythmia	ECG/AECG	50%	36%	19%	60%	30%	5.61
43	Mental status	Psychological health	0%	29%	31%	20%	28%	5.53
44	Mental status	Psychological health	0%	21%	23%	80%	28%	5.72
45	HRV	ECG/AECG	50%	43%	12%	40%	26%	5.29
46	Carotid ultrasound Vmax	PEC	0%	29%	19%	40%	23%	5.51
47	BNP	PEC	0%	36%	19%	40%	23%	5.43
48	Blood glucose	Added outcomes	0%	7%	23%	60%	21%	5.16
49	Blood pressure	CSS	0%	36%	8%	40%	19%	4.72

scored by all participants between rounds is used to determine the consistency of outcome selection. A previous COS study reported minimal changes in scores between the first and second rounds of Delphi survey^[24], indicating that additional rounds did not necessarily increase the degree of consensus for outcome selection. Hence, two rounds of Delphi surveys were performed in this study. Indeed, a two-to-three-round Delphi survey is

generally sufficient for reaching consensus on outcome selection.

This study has several strengths. First, it adopted a clear methodology and guidelines based on COS-STAD, COS-STAR, and COMET Handbook for outcome identification from various sources, including literature and clinical trial registry databases as well as clinician and patient questionnaires to generate an outcome pool and prelimi-

Table 5**Number of consensus achieved on outcomes in Delphi round 2.**

No.	Outcome	Domain	Number of consensus achieved	Ranking
1	Chest distress	CSS	4	1
2	Attack times	CSS	4	1
3	Duration	CSS	4	1
4	Nitroglycerin consumption	CSS	4	1
5	Cardiovascular event	LTP	4	1
6	Myocardial infarction	LTP	4	1
7	Unstable angina pectoris	LTP	4	1
8	Pain degree	CSS	3	2
9	SAQ	CSS	3	2
10	Cardiogenic death	LTP	3	2
11	Heart failure	LTP	3	2
12	TIB	ECG/AECG	3	2
13	Time to onset of chest pain	ETT	3	2
14	CTA coronary stenosis	PEC	3	2
15	Survival time	LTP	2	3
16	ST segment depression	ECG/AECG	2	3
17	Flatness or inversion of T wave	ECG/AECG	2	3
18	Duke score	ETT	2	3
19	Time to 1-mm ST-depression	ETT	2	3
20	Palpitation	CSS	1	4
21	Score of TCM syndrome	TCMO	1	4
22	Score of TCM symptoms	TCMO	1	4
23	All-cause mortality	LTP	1	4
24	Clinic visits	LTP	1	4
25	Coronary stent implantation	LTP	1	4
26	Number of leads with ST-depression ≥ 1 mm	ETT	1	4
27	Walking distance	6MWT	1	4
28	Arterial stiffness	PEC	1	4
29	Mental status	Psychological health	1	4

Table 6**Voting results of consensus meeting.**

Ranking	Outcome	Domain	Vote	Percentage
1	Attack times	CSS	27	100.00%
2	Duration	CSS	23	85.19%
3	Cardiovascular event	LTP	22	81.48%
4	Myocardial infarction	LTP	22	81.48%
5	Unstable angina pectoris	LTP	20	74.07%
6	Cardiogenic death	LTP	19	70.37%
7	Time to onset of chest pain	Time to onset of chest pain	19	70.37%
8	Chest distress	CSS	17	62.96%
9	Pain degree	CSS	17	62.96%
10	Score of TCM symptoms	TCMO	16	59.26%
11	CTA coronary stenosis	PEC	15	55.56%
12	SAQ	CSS	14	51.85%
13	Nitroglycerin consumption	CSS	13	48.15%
14	ST segment depression	ECG/AECG	13	48.15%
15	Duke score	ETT	13	48.15%
16	Score of TCM syndrome	TCMO	13	48.15%
17	TIB	ECG/AECG	12	44.44%
18	Time to 1-mm ST-depression	ETT	12	44.44%
19	Heart failure	LTP	10	37.04%
20	Survival time	LTP	10	37.04%
21	Flatness or inversion of T wave	ECG/AECG	10	37.04%
22	Number of leads with ST-depression ≥ 1 mm	ETT	10	37.04%
23	Walking distance	6MWT	10	37.04%
24	All-cause mortality	LTP	9	33.33%
25	Mental status	Psychological health	8	29.63%
26	Palpitation	CSS	7	25.93%
27	Clinic visits	LTP	5	18.52%
28	Arterial stiffness	PEC	5	18.52%
29	Coronary stent implantation	LTP	4	14.81%

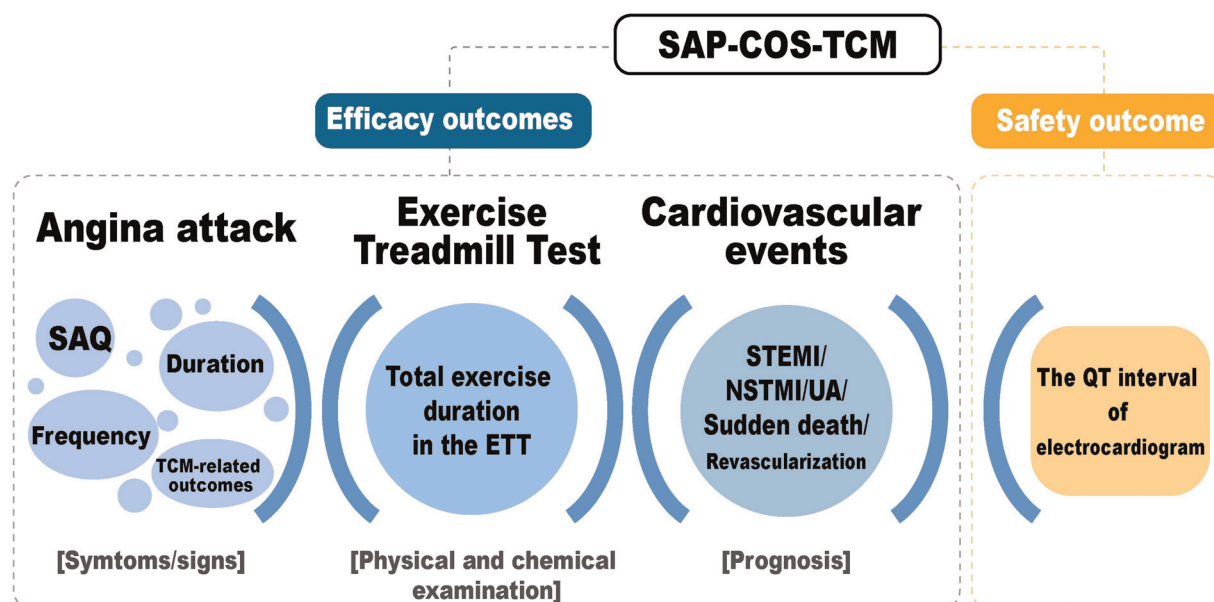


Figure 2. Core outcome set (COS) for stable angina pectoris in traditional Chinese medicine (TCM).

nary list of outcomes. Further, the size of the study population, which comprised participants and various stakeholder groups, was large. Anonymous voting (via an electronic app) during the consensus meeting was beneficial to prevent bias during voting. Second, the preliminary list of outcomes for the Delphi survey was reduced to 80 items to avoid response efficiency and maintain a certain response rate from participants during the process. Third, the COS development process was derived from clinical trials and based on the perspectives of clinicians and patients, highlighting its suitability for implementation in clinical research.

Several limitations of this study must be acknowledged. Studies with TCM-related interventions of acupuncture and Tuina were excluded, and only studies with medicinal interventions were included in the generation of the outcome pool. This may have caused some outcomes to be overlooked during the identification process. Further, as this study was completed in 2018, outcomes collected from various sources may not have been fully up-to-date (such as in 2016 and 2017). Moreover, representatives of different stakeholders for the consensus process were from China. This limits regional representation, which is necessary for the implementation of the COS at an international level.

Another limitation is the lack of specific standards or methods for calculating the weighted proportion of each stakeholder group in the consensus process. The number of participants from different stakeholder groups was balanced to ensure practicality. In this regard, the risk of selection bias and attrition bias was minimized by ensuring concordance between the proportion of a specific stakeholder group with the impact of that group on the outcomes. For example, major stakeholder groups such as healthcare professionals, clinicians, patients, and COS users would focus on clinically related outcomes that are more relevant to the final core outcomes. Hence, a larger proportion of participants from these major stakeholder groups were invited as compared to minor stakeholder groups, which may have reduced the impact of stakeholder groups with low attrition rate on the study results. High

attrition rates of 60.98% and 45.98% were noted in Delphi rounds 1 and 2, respectively. This is common in the Delphi process based on other COS developments. Therefore, a wide range of participants across several stakeholder groups was invited to achieve greater consistency in responses to the consensus process. The participant selection process may be improved by performing relevant power analyses. Further, reliability of the Delphi survey results can be determined by comparing responses from participants who joined and those who did not join the Delphi survey at the consensus meeting. The COS will be submitted for publication in peer-reviewed and open access journals. The results will be disseminated on the website for Chinese clinical trials of COS (<http://chicos.org.cn>).

5 Conclusions

This is the first study to develop a COS for SAP in TCM using Delphi and consensus methods. The final COS-SAP-TCM comprised four outcomes, namely, cardiovascular events (myocardial infarction, unstable angina pectoris, and sudden cardiac death), treadmill test duration, angina occurrence (frequency of angina occurrence, angina duration, Seattle angina scale), and QT interval. The COS-SAP-TCM developed in this study should be implemented in future research to reduce heterogeneity in outcomes and to improve the comparability and relevance of outcomes measured across different studies in a specific healthcare area.

Conflict of interest statement

Junhua Zhang and Boli Zhang are editorial board members of this journal. None of the other authors declare any conflicts of interest.

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Author contributions

Mingyan Zhang wrote the paper and conceived the project. Junhua Zhang provided general guidance for the protocol of the research. Hui Zi Chua contributed to the English translation of this protocol. Rui Feng was responsible for the systematic review. Meijuan Lu and Ying Tian conducted qualitative survey, the Delphi process and data interpretation. All authors edited and critically revised the study protocol. All authors have read, contributed to, and approved the manuscript.

Ethical approval of studies and informed consent

The study received ethical approval from the Ethics Committee of the Evidence-based Medicine Centre, Tianjin University of Traditional Chinese Medicine (TJUTCM-EC20170008). Informed consent was obtained from all participants who participated in the semi-structured interviews, questionnaires, and two rounds of the Delphi survey. The study is registered with the COMET Initiative (<http://www.cometinitiative.org/Studies/Details/391>).

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