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Core outcome set for intervention research on snakebite envenomation in South Asia

Soumyadeep Bhaumik ,[1,2] Deepti Beri,[1] Vishal Santra,[3] Maya Gopalakrishnan,[4] Mohammad Abul Faiz,[5] Paula R Williamson,[6] Mike Clarke,[7] Sanjib Kumar Sharma,[8] Jagnoor Jagnoor [9]

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[1]The George Institute for Global Health India, New Delhi, India
[2]Meta-research and Evidence Synthesis Unit, George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
[3]Society for Nature Conservation, Research and Community Engagement, Hooghly, West Bengal, India
[4]Department of Internal Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India
[5]Dev Care Foundation, Dhaka, Bangladesh
[6]Department of Health Data Science, University of Liverpool, Liverpool, UK
[7]Centre for Public Health, Queen's University Belfast, Belfast, UK
[8]Department of Internal Medicine, BP Koirala Institute of Health Sciences, Dharan, Nepal
[9]Injury Division, George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia

Correspondence to
Dr Soumyadeep Bhaumik; sbhaumik@georgeinstitute.org

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ABSTRACT

Background The 2019 WHO strategy to reduce snakebite burden emphasises the need for fostering research on snakebite treatments. A core outcome set (COS) is a consensus minimal list of outcomes that should be measured in research on a particular condition. We aimed to develop a COS for snakebite research in South Asia, the region with the highest burden.

Methods We used data from a systematic review of outcomes to develop a long list of outcomes which were rated in two rounds of online Delphi survey with healthcare providers, patients and the public, and potential COS users to develop a COS for intervention research on snakebite treatments in South Asia for five intervention groups. Subsequently, meetings, consultations and workshops were organised to reach further consensus. We defined the consensus criteria a priori.

Results Overall, 72 and 61 people, including patients and the public, participated in round I and round II of the Delphi, respectively. Consensus COSs (including definition and time points) were developed for interventions that prevent adverse reaction to snake antivenom (three outcomes), specifically manage neurotoxic manifestations (five outcomes), specifically manage haematological manifestations (five outcomes) and those that act against snake venom (seven) outcomes. A priori criteria for inclusion in COS were not met for COS on interventions for management of the bitten part.

Conclusion The COS contributes to improving research efficiency by standardising outcome measurement in South Asia. It also provides methodological insights for future development of COS, beyond snakebite.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a need for strengthening research on snakebite treatments in the South Asia. The region has the highest snakebite burden.
⇒ There is heterogeneity in outcomes and their measurements in trials on snakebite.
⇒ There is a need for developing a core outcome set (COS).

WHAT THIS STUDY ADDS

⇒ Consensus COSs (including definition and time points) for South Asian trials were developed for interventions that prevent adverse reaction to snake antivenom, specifically manage neurotoxic manifestations, specifically manage haematological manifestations and those that act against snake venom.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The COS will contribute to strengthening research by standardising outcome measurement in South Asia and making research more relevant and useful to healthcare workers and patients.
⇒ Beyond snakebite, the study provides insights for improving the standards for COS development (geographical context specification; stakeholder engagement) and highlights the need for the development of guidance and tools for patient and public engagement.

INTRODUCTION

The Global Burden of Disease study estimates 63 400 (95% CI 38 900 to 78 600) snakebite deaths for 2019, with about 80% in India and Pakistan.[1] In 2019, the WHO set the target to halve the burden of snakebite by 2030 and recognised the need for fostering research on snakebite treatment as a strategy towards 'ensuring safe, effective treatment of snakebite'.[2] Major funders, such as Wellcome Trust,[3] have committed investments for developing better treatments for snakebite. A 2022 landscape analysis[4] found that, since 2015, 196 candidate therapeutics (drugs and biologics) and 127 available immunoglobulin products (animal plasma/serum derived) had been researched for snakebite treatment. With a pipeline of candidate therapeutics, more intervention research on snakebite is imminent. Interest from snake antivenom (SAV) manufacturers might also be expected to increase to comply with Target Product Profiles (TPPs) for SAV being developed by the WHO.[5]

To the best of our knowledge, and published research at that time, our research group, in 2020, first identified[6] the need for developing a core outcome set (COS) for snakebite. A COS is a consensus-derived, minimal list of outcomes that should be measured in research or practice for a particular health condition. Apart from standardisation, which enables comparison, a COS also ensures that outcomes which are measured in research are relevant to not only researchers but also to healthcare workers, patients and other stakeholders,[7] thus, enabling research efficiency.[8 9]

We aimed to develop a COS for studies on snakebite management in South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan and Sri Lanka) for interventions that:

1. Prevent adverse reaction to SAV.
2. Are for management of the bitten part, for example, for the management of wounds, bacterial infections and or swelling of the limbs and compartment syndrome.
3. Are specific to management of neurotoxic manifestations, for example, ventilation-different modalities and neostigmine edrophonium.
4. Are specific to management of haematological manifestations, for example, blood products—different types, plasma exchange, heparin and recombinant factors.
5. Act against the snake venom.

We focused on South Asia due to its high burden of snakebites and similarities in the distribution of medically important snakes, health systems structure and a shared cultural history.[1] Unlike other health conditions, which are clinically similar globally (and thus a global COS has high usability), snakebite envenomation is a heterogeneous clinical condition. The clinical presentation and interventions for its management are dependent on snake species in a particular geographical area. It is for this reason that WHO develops region-specific practice guidelines and TPPs,[5 10] rather than global ones. By setting the scope of the COS to a region (South Asia), we aimed to develop a more contextually relevant and better-suited tool for use in future research to facilitate safe and effective treatment in the region. The categorisation of interventions into five different groups (in the aforementioned objectives) is in alignment with WHO-SEARO (South-East Asia Regional Office) guidelines for the management of snakebites.[10] The study was set up to develop a COS for each intervention category, allowing researchers and trialists to choose one that is appropriate to the intervention they are evaluating in their study.

METHODS

Study design

We developed the COS in three phases, in alignment with methods recommended by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative (https://comet-initiative.org). In phase I, we generated a list of initial outcomes for consideration in the COS through a global systematic review of outcomes.[11] In phase II, we conducted a two-round Delphi survey and a consensus meeting to finalise the outcomes to be part of the COS. Phase III comprised online consultation, followed by a workshop to reach a consensus on 'how' the outcomes in the COS should be measured. The three phases of the COS development are shown diagrammatically in figure 1.

Protocol, registration and reporting

We registered the study in the COMET database (https://comet-initiative.org/Studies/Details/1849) and developed the study protocol a priori. We report our compliance with the Core Outcome Set-STAndards for Reporting (COS-STAR) reporting guideline[12] in online supplemental appendix 1. There were no protocol deviations.

Study steering committee

A steering committee for the study included representatives of the COMET Initiative, healthcare workers and researchers from Bangladesh, India, and Nepal and a community practitioner from India, leading snakebite mitigation and prevention programmes (see the 'Acknowledgements' section). This committee members played an advisory role, providing inputs through emails and virtual meetings, and the members did not participate in the Delphi survey.

Phase I: obtaining a list of outcomes for Delphi

We generated the initial list of outcomes from a systematic review of outcomes (separately published[11]), which categorised outcomes as per a standard outcome taxonomy.[13] Based on the results, we confirmed, with the steering committee, the scope of the project to exclude the development of a COS for mental health interventions for snakebite, although it is an important area of concern.[14] For the reasons stated, we did not include the following types of outcomes, identified from the systematic review, in the Delphi survey:

- Psychiatric outcomes: deemed out of scope.
- Immunological or serology related (eg, venom concentration or antibody measurement): deemed as proxy, not relevant to clinical decision-making and not feasible.
- Composite outcomes: varied combinations, not validated in South Asia, impedes patient and public understanding and are difficult for healthcare communication.

We reviewed all remaining outcomes and merged those that are sufficiently similar, into a single item. We did this with the intent of limiting survey time to 30 min per round and avoiding confusion around similar outcomes (particularly in non-clinician

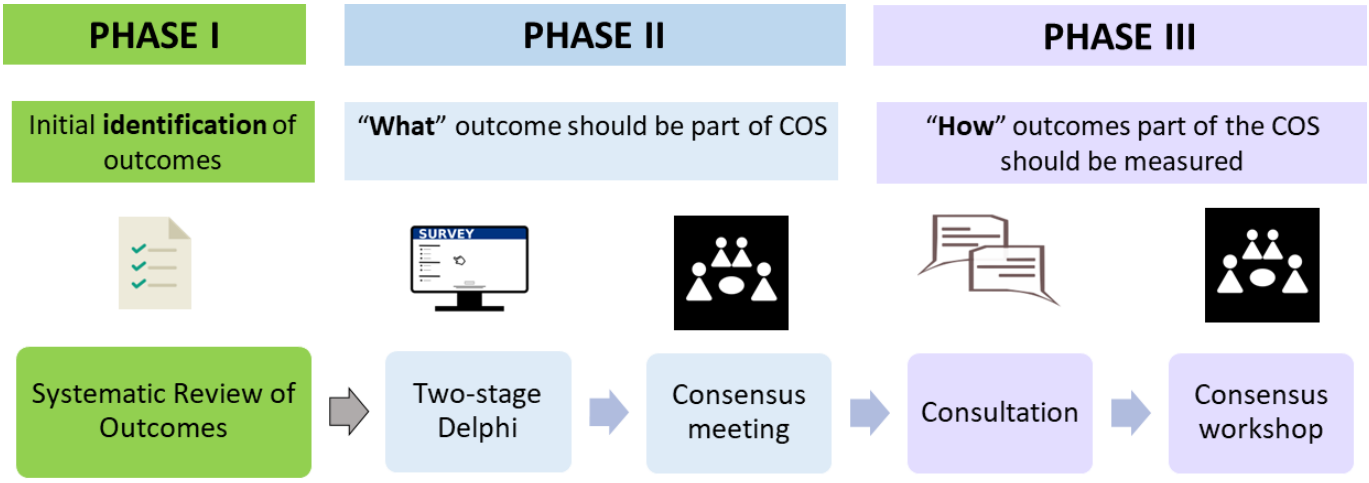

Figure 1 Development of core outcome set (COS) for intervention research on snakebite in South Asia.

health workers, patients and the public). Survey time is a key factor for participation, completion and retention in Delphi surveys.[15] Delphi participants could see details of each outcome entity by clicking on it. During the pilot phase, we conducted multiple rounds of testing on the survey tool to avoid ambiguity in language for the outcomes and to acquire feedback on instructions, presentation and time of completion (see the 'Acknowledgements' section).

Phase II: attaining consensus on 'what' outcomes should be part of the COS

Three groups of participants (18 years and above) participated in the Delphi survey:

1. Healthcare providers (clinicians, nurses, community health workers and social workers) involved in snakebite care.
2. Patients and the public (snakebite survivors, family members of a person who has experienced snakebite and representatives of communities affected by snakebite).
3. Potential COS users (researchers including trialists, venom researchers, systematic reviewers, journal editors, research funders and guideline developers).

All participants were from South Asia. For the 'potential COS user' category, those with an international scope of work related to snakebite also participated. The study was designed to be multilingual with options in Bangla, English and Hindi, primarily to enable participation of patients and the public.

We recruited participants through email (authors of published studies and trial registry records), recruitment posters (for patients and the public), email lists of snakebite-related organisations/networks and institutional social media accounts. All potential participants were introduced to the COS concept through a plain language summary and a COMET Initiative video.[16] Those who expressed interest were sent the participant information sheet and a link for registering in Delphi Manager, a web-based online system, through which the two-stage electronic Delphi survey was instituted.

In both rounds, participants rated outcomes on a Likert scale of 1–9 (wherein a rating of 1–3 corresponds to 'limited importance for decision-making'; 4–6 to 'important for decision-making, but not critical' and 7–9 to 'critical for decision-making') for five different modules, corresponding to the five interventions groups for which the COS was developed. During the Delphi voting, intervention modules appeared at random, with no fixed order.

In the first Delphi round, participants could suggest additional outcomes, for consideration of inclusion in the second round. We carried all outcomes from the first round and relevant additional outcomes (reviewed by the research team and steering committee member) to the second Delphi round. In the second round, participants saw their own ratings as well as group ratings for the three stakeholder groups and were asked to consider rescoring the outcomes. We defined consensus for the Delphi a priori as:

- Consensus of classification as a core outcome (consensus in): ≥70% of participants in all three stakeholder groups give a score between 7 and 9 (critical for decision-making) and ≤15% of participants in all three stakeholder groups give a score between 1 and 3 (of limited importance for decision-making).
- Consensus of classification as not being a core outcome (consensus out): ≥70% of participants in all three stakeholder groups give a score between 1 and 3 (of limited importance for decision-making) and ≤15% of participants in all three stakeholder groups give a score between 7 and 9 (critical for decision-making).
- No consensus: any other scoring.

If a participant skipped rating a particular outcome, we used the actual number of responses for each outcome to calculate the proportions. We invited those who participated in both the rounds of the Delphi to attend an online consensus meeting. For outcomes on which there was 'no consensus' after two rounds, the participants deliberated and voted to achieve consensus as per the following a priori criteria:

- Consensus in: >70% of meeting attendees marked it as critical for decision-making.
- Consensus out: ≤70% of meeting attendees marked it as critical for decision-making.

Phase III: developing consensus recommendations on 'how' outcomes in the COS should be measured

We were guided by the principles of the COnsensus-based Standards for the selection of health Measurement Instruments guidance to develop consensus recommendations on how outcomes in COS should be measured.[17] The minimum criteria for choice were to have good content validity (including face validity), good internal consistency (if applicable) and be feasible in the South Asian Context. In addition, we also considered reliability and responsiveness (if applicable).

We listed options for 'how' outcomes in the COS should be measured (including different definitions available and relevant time points for each included outcome) in a tabular manner noting details about its content validity, internal consistency, feasibility and reliability and responsiveness of each tool. For this purpose, we use information from the systematic review conducted in phase I, and additionally conducted focused literature searches, as relevant. We shared the document with participants online, for consultation for 15 days giving them time to comment, modify and edit our document on any aspect. Subsequently, an online workshop was organised where the COS with measurement recommendations (definitions and time points) was finalised. We had planned to do voting should there be no consensus, among participants, but this was not necessary.

Patient and public involvement

Patients and the public were involved, as described in preceding subsections of methods.

RESULT

Study participants

The Delphi survey took place during August–October 2022. A total of 81 participants registered in the Delphi Manager platform, out of which 9 did not participate in the survey (ie, did not rate any outcome). Overall, 72 participants completed the first round, and 61 participants (84.7% of the 72) completed the second round. In the first round, four (5.5% of 72) participants did not rate outcomes in all five intervention modules. The corresponding number in the second round was two (3.2% of 61). Characteristics of Delphi participants are presented in table 1.

Consensus on 'what' outcomes should be part of COS

After the first round, consensus was achieved on the inclusion of one outcome in the intervention specific to the neurological manifestations module, and two outcomes in the interventions that target snake venom module. For all other outcomes, no consensus was attained.

Table 1 Characteristics of participants in Delphi Survey

Stakeholder group	Round 1 of Delphi	Round 2 of Delphi	Retention, %
Healthcare provider	**34 (male: 29; female: 5)** ► Clinician: 31 ► Nurse: 2 ► Social worker: 1	**30 (male: 25; female: 5)** ► Clinician: 27 ► Nurse: 2 ► Social worker: 1	**88.2***
Patient or public	**12 (male: 8; female: 4)** ► Snakebite survivor: 5 ► Family member: 5 ► Community representative: 2	**11 (male: 8; female: 3)** ► Snakebite survivor: 5 ► Family member: 4 ► Community representative: 2	**91.7†**
Potential COS user	**26 (male: 18; female: 8)** ► Guideline developer: 3 ► Journal editor: 1 ► Research funder: 1 ► Researchers: 21	**20 (male: 13; female: 7)** ► Guideline developer: 2 ► Journal editor: 1 ► Research funder: 0 ► Researchers: 17	**76.9‡**

*In round 1, the country-wise distribution of participants was Bangladesh: 2, Bhutan: 1, India: 29, Nepal: 1, Pakistan: 1 and Sri Lanka: 0. In round 2, 4 participants from India dropped out.
†All participants from the patient or public representative stakeholder group were from India. In round 2, 1 participant dropped out.
‡In round 1, the country-wise distribution of participants was Bangladesh: 2, Bhutan: 0, India: 12, Nepal: 4, Pakistan: 0, Sri Lanka: 2 and other countries: 6. In round 2, 1 participant from Bangladesh, 3 from India and two from other countries dropped out.
COS, core outcome set.

We reviewed 16 free-text responses from 8 participants with regard to additional outcomes and included 1 for rating in the second round which was—outcomes specific to viper bites (capillary leak syndrome, thrombotic microangiopathy and adrenal/pituitary insufficiency). Details on suggestions received and reasons for their inclusion or exclusion in the next round are presented in online supplemental appendix 2 .

After the second Delphi round, a 'consensus in' status was obtained for two outcomes in the preventing adverse reaction intervention module, four outcomes in intervention specific to neurological manifestations module, two outcomes in intervention specific to haematological manifestations module, and five outcomes in interventions that target snake venom. In both the rounds, no consensus attained 'consensus out' status.

The results of the Delphi rounds with scores were sent to all participants who completed both rounds, before the online consensus meeting. A total of 13 (10 male and 3 female) participants from Bhutan (1), India (9), Sri Lanka (1), Malaysia (1) and Australia (1) attended the consensus meeting. No patient or public stakeholder joined the meeting. All outcomes in the 'no consensus' category were discussed and voted on to achieve the final decision regarding inclusion or exclusion for the COS. A summary of different consensus decisions in the two rounds of Delphi, with detailed scoring is presented in online supplemental appendix 3.

Consensus recommendations on 'how' outcomes in the COS should be measured

In this phase of the project, 16 people (including 3 who expressed intent to join the consensus meeting on 'what' outcomes should be part of COS but were unable to attend the meeting at the last minute) participated. In the online consultation, the participants reviewed and discussed 'how' the outcomes included in the COS should be measured. Overall, we received 203 responses during this consultation, including suggested edits, notes on agreement and disagreements, discussion on preference parameters, definitions and time points of measurement. After the online consultation, there was unanimous consensus on outcome definitions for:

- All three outcomes in preventing adverse reaction intervention COS.
- All, but two, outcomes in intervention specific to neurological manifestations COS.
- All five outcomes in intervention specific to haematological manifestations COS.
- All, but one, outcome in interventions that target snake venom COS.

In the final online workshop, the participants discussed all pending issues to arrive at a consensus on all aspects of how the core outcomes should be measured in future intervention studies. The final COS for intervention research for different intervention groups, along with recommendations for measurement, is presented in table 2.

DISCUSSION

Summary of key findings

In this study, we developed a COS of what and how outcomes should be measured in future intervention research on snakebite in South Asia in four domains. The COSs are on interventions that prevent adverse reaction to SAV (three outcomes), specifically for the management of neurotoxic manifestations (five outcomes), specifically for the management of the haematological manifestations (five outcomes) and on interventions that act against snake venom (seven outcomes).

Study findings in broader context of snakebite research

Setting the scope for COS for snakebite is challenging. Snakebite is a heterogeneous condition, dependent on the varying distribution of species geographically and consequent variability in interventions. A very narrow geographical scope of COS would have a very well-defined context, with few conflicting opinions on what should and should not be part of the COS. However, the relevance of such a COS might be limited to trials in the specific geographical area or population only. On the other hand, a very wide geographical COS would be contextually less relevant, with challenges in achieving consensus (leading to agreement on the inclusion of too many or too few outcomes), thus hampering its utility and applicability. We contend that a regional scope based on similarity in geographical species, health systems and shared sociocultural history, as was done in our COS,

Table 2 Core outcome set (COS) for intervention research on different intervention types

Consensus 'what' outcomes part of COS	Consensus recommendation on 'how' outcomes part of COS should be measured	
	Outcome definition	**Time point**
COS for research on interventions that prevent adverse reaction to snake antivenom		
Anaphylaxis or early antivenom reaction (develops immediately or within hours of administering snake antivenom)	**Definition:** Proportion of people with anaphylaxis as defined by World Allergy Organization Anaphylaxis Guidance 2020* **Data type:** Dichotomous Definition is available in Table 2/ Figure 1/ of Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100 472.	► 6 hours from randomisation, for randomised controlled trials (RCTs). ► 6 hours from intervention, for other non-randomised intervention designs
Death (all-cause/cause-specific)	**Definition:** All-cause mortality **Data type:** Dichotomous	► 4 weeks (28 days) from randomisation, for RCTs. ► 4 weeks (28 days) from intervention, for other non-randomised intervention designs
Requirement of ICU (intensive care unit) admission and/or duration of ICU stay	**Definition:** Proportion of patients who were admitted to ICU **Data type:** Dichotomous **Note**: Studies should clearly report the specific criteria used for ICU admission and discharge in trial sites	► 4 weeks (28 days) from randomisation, for RCTs. ► 4 weeks (28 days) from intervention, for other non-randomised intervention designs
COS for research on interventions for management of the bitten part, for example, for the management of wounds, bacterial infections and or swelling of the limbs, compartment syndrome		
Consensus was not obtained for any outcome		
COS for research on interventions specific to management of neurotoxic manifestations, for example, ventilation-different modalities, neostigmine, edrophonium		
Consensus 'what' outcomes part of COS	**Consensus recommendation on 'how' outcomes part of COS should be measured**	
	Outcome definition	**Time point**
Death (all-cause/cause-specific)	**Definition:** All-cause mortality **Data type:** Dichotomous	► 4 weeks (28 days) from randomisation, for RCTs. ► 4 weeks (28 days) from intervention for other non-randomised intervention designs
Neuro-muscular paralysis	**Definition**: Time taken for complete reversal of paralysis in at least one of the two muscle groups (extraocular and bulbar) and respiratory paralysis **Data type:** time to event **Note**: Outcome assessors should be mandatorily trained and a standard operating procedure developed for the purpose.	Not applicable.
Respiratory distress (breathing problem):	**Definition:** Proportion of patients with severe respiratory distress, which is defined† by, having any one of below 1. Talks in words (ie, in not phrases or sentences) 2. Accessory muscles being used 3. Oxygen (O2) saturation (on air) <92% 4. Respiratory Rate(RR)<12/min or >20/min 5. Partial pressure of carbon dioxide (PaCO2)>45 mm Hg 6. Single breath count (number of digits counted in one exhalation) <25 **Data type**: Dichotomous	► 24 hours from randomisation, for RCTs ► 24 hours from intervention, for other non-randomised intervention designs
Duration of mechanical ventilation	**Definition:** Time in hours the person is in mechanical ventilation(initiation of ventilatory support to the onset of weaning.) **Data type:** time to event **Note:** Studies should clearly report criteria for use of mechanical ventilation, both its onset and termination.	Not applicable.
Duration of ICU stay	**Definition:** Time from admission to discharge from ICU—in hours **Data type:** time to event **Note**: Studies should clearly report the specific criteria used for ICU admission and discharge in trial sites.	Not applicable.
COS for research on interventions (treatments) specific to management of the haematological (blood) manifestations, for example, blood products—different types, plasma exchange, heparin and recombinant factors		
Consensus 'what' outcomes part of COS	**Consensus recommendation on 'how' outcomes part of COS should be measured**	
	Outcome definition	**Time point**
Death (all-cause/cause-specific)	**Definition:** All-cause mortality **Data type:** Dichotomous	► 4 weeks (28 days) from randomisation, for RCTs. ► 4 weeks (28 days) from intervention for other non-randomised intervention designs
Duration of ICU stay	**Definition:** Time from admission to discharge from ICU—in hours **Data type:** time to event **Note:** Studies should clearly report the specific criteria used for ICU admission and discharge in trial sites	**Time point**: not applicable

Continued

Table 2 Continued

COS for research on interventions (treatments) specific to management of the haematological (blood) manifestations, for example, blood products—different types, plasma exchange, heparin and recombinant factors		
Bleeding	**Definition:** Proportion of people developing major haemorrhage, as defined by the International Society on Thrombosis and Haemostasis as (1) fatal bleeding, (2) symptomatic bleeding in a critical organ, (3) bleeding resulting in a drop in haemoglobin >20 g/L or (4) requiring 2 or more units of whole blood or red cell blood transfusion. **Data type:** Dichotomous	► 24 hours, 48 hours and 7 days from randomisation, for RCTs. All time points should be reported. ► 24 hours, 48 hours and 7 days from intervention for other non-randomised intervention designs. All time points should be reported.
Blood clotting and blood coagulability	**Definition**: Proportion of patients with abnormal blood coagulability, assessed by the whole blood clotting test (20 WBCT)‡ **Data Type**: Dichotomous **Note**: Only a single-use clean, dry, glass test tube should be used for the test. There is no clinical evidence indicating validity of the test when plastic containers are used. Outcome assessors should be blinded, trained and a standard operating procedure developed for the purpose.	► 6 hours, 12 hour, 24 hours and 7 days§ from randomisation, for RCT. All time points should be reported. ► 6 hours, 12 hours, 24 hours and 7 days§ from intervention for other non-randomised intervention designs. All time points should be reported.
Acute kidney failure/injury or requirement of dialysis	**Definition**: Proportion of patients who develop AKI, as defined by the KDIGO diagnostic criteria should be met (any one of the three): 1. An increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours 2. An increase in serum creatinine to ≥1.5 times baseline within the previous 7 days 3. Urine volume ≤0.5 mL/kg/hour for 6 hours **Data type:** Dichotomous	► 4 weeks (28 days) from randomisation, for RCTs. ► 4 weeks (28 days) from intervention for other non-randomised intervention designs
COS for research on interventions (treatments) that act against the snake venom		
Consensus 'what' outcomes part of COS	**Consensus recommendation on 'how' outcomes part of COS should be measured**	
	Outcome definition	**Time point**
Death (all-cause/cause-specific)	**Definition:** All-cause mortality **Data type:** Dichotomous	► 4 weeks (28 days) from randomisation, for RCTs. ► 4 weeks (28 days) from intervention for other non-randomised intervention designs
Anaphylaxis or early antivenom reaction (develops immediately or within hours of administering snake antivenom)	**Definition:** Proportion of people with anaphylaxis as defined by World Allergy Organization Anaphylaxis Guidance 2020* **Data type:** Dichotomous **Note:** Available in table 2/figure 1 of Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100 472.	► 6 hours from randomisation, for RCTs. ► 6 hours from intervention, for other non-randomised intervention designs
Respiratory distress (breathing problem)	**Definition**: Proportion of patients with severe respiratory distress, defined† by having any one of below 1. Talks in words (ie, in not phrases or sentences) 2. Accessory muscles being used 3. Oxygen(O2) saturation (on air) <92% 4. Respiratory Rate (RR) <12/min or >20/min 5. partial pressure of carbon dioxide (PaCO2) >45 mm Hg 6. Single breath count (number of digits counted in one exhalation) <25 **Data type:** Dichotomous	► 24 hours from randomisation, for RCTs ► 24 hours from intervention, for other non-randomised intervention designs
Requirement of mechanical ventilation	**Definition:** Proportion of patients requiring mechanical ventilation **Data type:** Dichotomous **Note:** Studies should clearly specify the criteria for deeming a patient requiring mechanical ventilation. This criterion can be used in facilities with no mechanical ventilation too.	► 48 hours from randomisation, for RCTs. ► 48 hours from intervention for other non-randomised intervention designs
Bleeding	**Definition:** Proportion of people developing major haemorrhage, as defined by the International Society on Thrombosis and Haemostasis as (1) fatal bleeding, (2) symptomatic bleeding in a critical organ, (3) bleeding resulting in a drop in haemoglobin >20 g/L or (4) requiring 2 or more units of whole blood or red cell transfusion. **Data type:** Dichotomous	► 24 hours, 48 hours and 7 days from randomisation, for RCTs. All time points should be reported. ► 24 hours, 48 hours and 7 days from intervention for other non-randomised intervention designs. All time points should be reported.
Blood clotting and blood coagulability	**Definition:** Proportion of patients with abnormal blood coagulability, assessed by the 20 WBCT‡ **Data type:** Dichotomous **Note:** Only a single-use clean, dry, glass test tube should be used for the test. There is no clinical evidence indicating validity of the test when plastic containers are used. Outcome assessors should be blinded, trained and a standard operating procedure developed for the purpose.	► 6 hours, 12 hours and 24 hours, from randomisation, for RCTs. All time points should be reported. ► 6 hours, 12 hours and 24 hours, from intervention for other non-randomised intervention designs. All time points should be reported.

Continued

Table 2 Continued

COS for research on interventions (treatments) that act against the snake venom		
Acute kidney failure(AKI)/injury or requirement of dialysis	**Definition:** Proportion of patients who develop AKI, as defined by the KDIGO diagnostic criteria should be met (any one of the three) 1. An increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours 2. An increase in serum creatinine to ≥1.5 times baseline within the previous 7 days 3. Urine volume ≤0.5 mL/kg/hour for 6 hours **Data type:** Dichotomous	► 4 weeks (28 days) from randomisation, for RCTs. ► 4 weeks (28 days) from intervention for other non-randomised intervention designs

*The World Allergy Organization definition is widely recognised globally and endorsed by 52 national professional organisations, including in South Asia by the Indian College of Allergy and Applied Immunology, and Pakistan Allergy Asthma and Immunology Society.
†This is a consensus-derived definition based on the review of guidelines for acute respiratory distress (GINA) and snakebite by the Ministry of Health and Family Welfare, India, and in alignment with broader principles of respiratory physiology. Respiratory distress (breathing problem) though related to neuroparalysis was seen as an important outcome for decision-making. However, for snakebite, and in South Asia, no robust validated tool is available. The consensus derived criterion included clinical measures, such that the evidence generated is in alignment with existing clinical practice in South Asia, and that trials on snakebite ought to be carried out in primary health centres, where advanced equipment might not be available. The criterion is designed, such that it can be used for all patients, irrespective of intubation status.
‡The 20 WBCT was chosen because it is simple to measure, and evidence developed from trials, using it as an outcome would directly translate to practice in the South Asian context. A recent systematic review(*Lamb T, Abouyannis M, de Oliveira SS, *et al*. The 20 min whole blood clotting test (20 WBCT) for snakebite coagulopathy-A systematic review and meta-analysis of diagnostic test accuracy. PLoS Negl Trop Dis. 2021 Aug 10;15(8): e0009657) found that WBCT 20 is a highly specific and fairly sensitive bedside test for detecting coagulopathy in snakebite. It should also be noted that a COS is a minimal standard, and trialist might choose other measures (eg, international normalised ratio or INR), should resources be available, but such measures do not translate directly for practice in primary health centres and many under-resourced secondary and tertiary hospitals (which do not have 24 X 7 laboratory support), which is where people affected by snakebite present to. Inclusion of WBCT 20, in the COS enables conduct of trials in wider types of health facilities.
§Time point of 7 days is recommended only for specific species, which cause long-term or recurrent coagulopathy. An indicative list is provided below:
► *Trimeresurus erythrurus* (spot tailed/red tailed green pit viper).
► *Rhabdophis subminiatus* (red-necked keelback).
► *Trimeresurus salazar* (Salazar's pitviper).
► *Naja kaouthia* (Monocle cobra).
► *Naja naja* (Spectacled cobra).
► *Daboia russelii* (Russell's viper).

achieves the right balance. For snakebite, another research group has developed a global COS[18] but this is might not be 'fit for purpose' in specific regions, such as South Asia. A global COS is conceptually problematic for snakebite. It is not in alignment with other ecosystem initiatives that seek to balance between heterogeneity and standardisation, through a regional basis of work. For example, standards around clinical practice or production of therapeutics are developed on a regional basis by the WHO.[5 10] Furthermore, in contrast to the global COS, which focuses on therapeutics against snake venom alone, our COS includes several types of interventions, thus enhancing its utility.

In interpreting and using the findings of the COS on interventions for the management of the bitten part, it is worthwhile noting that the intervention group consists of three distinct aspects: wound management, bacterial infections and swelling of the limbs. We reflect that this broad scope might have prevented achieving consensus. For the future, we recommend development of separate COS for the three aspects separately. In the interim, trialists and systematic reviewers working in this area might consider inclusion of the three outcomes that would have been included if we had lowered the threshold from 70% to 50%. These are oedema or swelling (localised around the area/extremity in which the bite has occurred), requirement of any type of surgery and impact on life after snakebite (functional impact, disability, quality of life, extremity function and recovery).

Strengths and weakness of the study

We followed standard methods of COS development[7 19] and reported in accordance with the COS-STAR guidelines.[12]Involvement of stakeholders was in alignment with the scope, relevancy of COS for multiple types of interventions and provision of clear recommendations on how to measure outcomes enhanced the utility of our COS. The number of outcomes in each intervention module in our COS is relevant and reasonable.

We faced considerable challenge in achieving greater involvement of patients and the public. We did anticipate the challenge, and therefore, designed our study to be multilingual, with options to participate in Bangla, English or Hindi. However, despite the multilingual option, extensive promotion through recruitment posters in multiple communities in India (we did not do so in other countries), and social media acceleration, we could recruit only 12 participants in this group. There was no patient participation in phase 3. While the Delphi approach does not depend on statistical power, a minimum number of 10 participants are considered necessary to give reliable results.[20–22] We did achieve this number for all intervention modules except one, which the participation of patient and public group was suboptimal. Four participants skipped the module on interventions that are specific for management of haematological manifestations, in entirety. Two of these participants noted that this was because they did not experience haematological manifestations. We believe participation in the patient and public group was impeded overall because of multiple reasons: absence of lived experience around outcomes or intervention groups, digital nature of the Delphi and the low levels of education in people who are most affected by snakebite. Four snakebite survivors who expressed interest could not differentiate between ratings for the importance of outcomes versus ratings for the severity of outcomes. Despite our endeavours, we were unsuccessful in communicating that importance and severity, although related, are not the same. For the future, we recommend methodological research to support and improve patient and public participation in COS development for conditions, such as snakebite, which primarily affects those with little or no education and people deprived of health literacy.

Other methods that can be tested are—interviewer-administered Delphi, the use of graphical visual cards and interactive animation with native language audio to support the Delphi survey. There is also a need for providing more

guidance for the patients and public group on deciding how to measure outcomes, where discussions are highly technical in nature. We tried to mitigate this by asking a member of our steering committee, who is a community practitioner leading a snakebite mitigation and prevention programme, to join the consensus meeting. We acknowledge gender imbalance in terms of less participation of female health workers. We also note the limited participation of nursing staff.

Methodological insights for future development of COS, beyond snakebite

The COS-STAD[19] sets the minimum standards for COS developers to follow and COS users to evaluate methodological rigour. We suggest that future iterations of COS-STAD should consider adding a standard around geographical region within the scope specification domain. Such a specification is not only important for conditions like snakebite which have clear geographical variation, but also for other health conditions where variation in cultural preferences and health systems is important.

The COS-STAD guideline[19] might also be revised to have more nuanced standards to ensure that COS development happens through the meaningful involvement of stakeholders from high burden and endemic nations. A recent systematic review found that only 20% of COS included LMIC participants.[23] It is known that non-involvement or tokenistic involvement of appropriate stakeholders decreases the utility, acceptance and uptake of COS.[24 25] Setting a standard for representative participation will fill this gap and contribute towards the larger challenge of poor stakeholder engagement and low uptake of COS in most research areas.

For many neglected tropical diseases and acute medical emergencies (not linked to chronic disease), such as snakebite, there are no organised survivor groups that can support recruitment in COS development. This is also true for many chronic conditions in low-income and middle-income countries. The current strategy of the COMET People and Patient Participation, Involvement and Engagement (PoPPIE) Working Group for involvement and engagement is predominantly focused on patient organisations.[26] Guidance and tools for community engagement might be developed by the COMET-POPPIE group to enable future COS development.

Future work on COS and outcomes for snakebite research in South Asia

To enhance the uptake of our COS, the core study team will develop a strategy to increase awareness, engage with potential users and promote the adoption of COS in the wider evidence ecosystem, as recent work on the area of COS uptake has suggested.[8 9 24 25] We will engage with national research funders (such as Bangladesh Medical Research Council, Indian Council of Medical Research, Nepal Health Research Council, Pakistan Health Research Council), professional bodies, medical journals and clinical trial registries (Indian and Sri Lankan) in South Asia to endorse and promote the uptake of this COS for future intervention research on snakebite. During our phase III discussions, numerous challenges and issues around the measurement of outcomes in intervention research on snakebite were raised. A by-product of this study is the formulation of an epistemic community of clinicians and COS users, who hope to work together on a position statement noting challenges and a research agenda on outcome measurement for snakebite trials. We will audit clinical trials conducted on snakebites in South Asia, 3 years after publication of the COS to evaluate the effect of the COS we developed and adjust strategies for its uptake.

CONCLUSION

The Delphi process resulted in the development of a COS for snakebite research in South Asia, which would enable standardisation of outcomes, facilitate meaningful comparisons and improve efficiency in research in the South-Asian region. Our research has also led to methodological insights, particularly around development standards of COS, and patient and public engagement.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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ORCID iDs
Soumyadeep Bhaumik http://orcid.org/0000-0001-9579-4453
Jagnoor Jagnoor http://orcid.org/0000-0002-5276-9095

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