Core outcome set for research in necrotising soft tissue infection patients: an international, multidisciplinary, modified Delphi consensus study

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Abstract
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Introduction: Necrotising soft tissue infections (NSTI) are serious infections associated with considerable morbidity and mortality. Heterogeneity of outcome reporting in the NSTI literature precludes the synthesis of high-quality evidence. There is substantial interest in studying the efficacy of hyperbaric oxygen treatment as an adjunctive treatment in NSTI. The aim of this study was to develop a set of core outcome measures for future trials evaluating interventions for NSTI.
Methods: A modified Delphi consensus method was used to conduct a three-round survey of a diverse panel of clinicians and researchers with expertise in NSTI, and patients with lived experience of NSTI. Participants rated the preliminary list of outcomes using a 9-point scale from 1 (least important) to 9 (most critical). The *a priori* definition of consensus required outcomes to be rated critical (score ≥ 7) by ≥ 70% of participants, and not important (score ≤ 3) by ≤ 15% of participants. After meeting consensus, outcomes were removed from subsequent rounds. Outcomes that did not meet consensus were included in subsequent rounds.
Results: Ninety-eight participants from 14 countries registered and 86%, 69% and 57% responded for each round, respectively. Outcome measures quantifying five core areas achieved consensus: Death, surgical procedures of debridements and amputations, functional outcome among survivors, measures of sepsis, including septic shock and organ dysfunction and resource use measured through length of hospital and intensive care unit stay.
Conclusions: This initial core set of outcome measures will be evaluated and optimised and can harmonise outcome measurements for investigations among patients with NSTI.

Introduction

Necrotising soft tissue infections (NSTI) are a group of rapidly progressive infections that can result in the destruction of skin, fat, fascia and muscle tissue and encompasses necrotising fasciitis, Fournier's gangrene, necrotising cellulitis and necrotising myonecrosis.[1] NSTIs are associated with considerable rates of morbidity and mortality, with a large Danish registry-based study demonstrating all-cause mortality rates of 19% at 30 days, 25% at 90 days and 30% at one year.[2] The cornerstones of treatment include urgent surgical debridement, broad-spectrum antibiotics and organ support in intensive care. Adjuvant therapies including hyperbaric oxygen treatment and intravenous immunoglobulin administration may also be used.[1]

A recent systematic review highlighted significant heterogeneity of outcomes reported in NSTI literature, with 311 different outcomes identified.[3] This profound heterogeneity precludes the synthesis of data for meta-analysis and the generation of high-quality evidence to assess interventions for NSTI. There has not previously been any standardisation or consensus amongst stakeholders regarding outcome measures that should be collected and reported in studies evaluating potential interventions for NSTI.[4] There is an urgent need to develop a core outcome set (COS) for use in all future clinical NSTI research.

A COS is a standardised set of outcomes that should be measured and reported on, as a minimum, in clinical trials of a specific condition or area of healthcare.[5] Standardisation of reportable outcomes improves the quality of trials and uniformity of data across centres, enabling critical comparison and analysis to improve research efficiency.[5] The use of a standardised COS also limits reporting bias which may occur via variable inclusion of selected outcomes, an issue that may be particularly relevant to NSTI research given the rarity of disease, and the variability in treatment practices.[1,5,6] Importantly, the use of standardised outcome sets enables higher quality evidence to substantiate and support the clinicians' choice of therapeutic interventions.

Hyperbaric oxygen treatment (HBOT) has been used in the treatment of NSTI since the 1960's and multiple observational studies indicate that this intervention strongly correlates with improved survival, particularly in the most severely unwell NSTI patients.[6,7] However, synthesis and interpretation of existing studies have been limited by marked heterogeneity of outcomes measured and uncertainty remains amongst the expert medical community regarding the role of HBOT for NSTI; uptake of this intervention is therefore highly variable and the establishment of a COS for NSTI would provide clarification and, hopefully, greater consensus on the utility of HBOT for NSTI.[3,6,8,9]

The objective of this study was to develop a COS for NSTI to be added to the Core Outcome Measures in Effectiveness Trials (COMET) database, by using a modified Delphi process to establish consensus across a group of key stakeholders. The aim is to improve consistency of reporting, reduce risk of reporting bias and enable higher quality meta-analyses. Ultimately, standardisation of core outcome reporting will enable more precise evaluation of treatment interventions and medical treatment decisions in the management of NSTI.

Methods

We obtained institutional ethics approval (447/23) from the Alfred Health Ethics Committee. Panel members were invited and presented with written information regarding the proposed study. Consent was implied by those who responded to the invitation and registered their details electronically.

STUDY DESIGN

We conducted a three-round modified Delphi consensus process to identify a recommended core outcome set for NSTI. The Delphi technique is widely used and allows for anonymous expert input while ensuring equal consideration of all opinions and synthesis of collective opinion on an international scale.[5,9,10] The study was registered *a priori* with the Core Outcome Measures in Effectiveness Trials (COMET; www.comet-initiative.org/delphimanager) Initiative. The surveys were hosted online via the COMET Initiative's DelphiManager software from the University of Liverpool, and sent to international clinicians and researchers with expertise in NSTI, as well as to patients with lived experience of NSTI and their caregivers.

The outcomes assessed encompass five core areas; death, physiological/clinical, life impact, resource use, and adverse events consistent with the taxonomy and outcome classification recommended by Dodd, et al.[9,11] Outcome measures were listed by core areas and presented sequentially in the survey. Survey respondents were a diverse panel of experts, fully anonymised and provided with key summarised information after each round. The proposed Delphi protocol aligned with the Core Outcome Set-STAndards for Development (COS-STAD) recommendations and was reviewed by Delphi experts and international experts in NSTI.[5,12]

PARTICIPANT RECRUITMENT

An expert Delphi panel was established to determine the COS for NSTI. A combined sampling strategy was used to recruit expert panel members to achieve a diverse representation of relevant stakeholders; clinicians, researchers and NSTI survivors or caregivers. A non-probability purposive sample of participants was recruited for the study. Given the variable global incidence and impact of NSTI and the objective to develop a COS of international applicability and validity, local and international researchers and clinicians were invited.[1,12] Researchers were identified from established NSTI research networks such as INFECT study group (an International and Multidisciplinary Project on Necrotizing Soft Tissue Infections, with 14 multidisciplinary partners from across Europe, Israel and the USA) the Collaborative Hyperbaric Medicine and Extreme Environment Research Association (CHYMAERA) network's necrotising infections subcommittee, and corresponding authors of peer-reviewed NSTI studies identified via systematic review. To encourage representation and participation from low- and middle-income countries, we invited NSTI stakeholders from different countries and the National Institute for Health and Care Research Global Health Research Unit on the Global Surgery India Hub. Clinicians with expertise in the management of NTSI were recruited from various specialty departments including plastic surgery, hyperbaric, infectious diseases, general surgery, and intensive care medicine.

Survivors or caregivers with personal experience of NSTI were included in the Delphi study to ensure shared decision-making during the process, and to appropriately reflect outcomes of importance to all stakeholders.[5,12] Survivors or caregivers were approached via online NSTI survivor support groups and Alfred Health NSTI consumers.

Participation was open to all relevant stakeholders and snowball sampling was utilised.[13] Research centres and departments were encouraged to invite additional qualified colleagues or survivors with experience in NSTI to contribute to the study.

Participants were invited to join the study through email correspondence and were provided with an information statement about the study objectives and requirements. Consent was implied by registration and participation via DelphiManager. There was no formal process of withdrawal of consent, but a degree of attrition was expected. All participants were at least 18 years old and identified as a relevant stakeholder in the NSTI field. Demographic information about panel members were collected on DelphiManager and customised to this study.

OUTCOME MEASURES

Generation of preliminary list of outcome measures

A systematic review was performed prior to this Delphi study to generate a comprehensive inventory of outcome measures reported in studies published from 2010 to 2020.[3] Three hundred and seventy-five studies were identified including 311 outcome measures which were reported and categorised into 11 outcome domains and five core areas, consistent with the taxonomy recommended by Dodd, et al.[11] The investigator group reviewed the list of outcomes identified in the systematic review and determined a shortlist of 50 outcomes to be presented to the expert panel. Non-specific outcome measures not feasible for collection in future large-scale clinical trials or highly case-specific outcomes which could not be generalised to all NSTI research or to limb or abdominal/pelvis NSTI, were excluded from the list. The 50 outcome measures were tabulated, written in non-technical language and provided to participants in the following core areas: Mortality/Survival (7), Physiological/Clinical (11), Life Impact (4), Resource Use (13), Adverse Events (3) for Round 1 of the Delphi study. Where applicable, additional information was listed under Help Text on DelphiManager to elaborate on specific scoring systems or outcome measures for participants.

Limb and abdomen and pelvis specific core outcome measures

Interventional and anatomically specific outcomes which were considered only relevant to NSTI of either the limbs (4) or abdomen and pelvis (8) were listed separately for consideration in additional sub-group outcome sets.

MODIFIED DELPHI PROTOCOL

Invited participants were emailed a link to register their details. Survey links were distributed to registered participants via the DelphiManager software platform; with each round of the survey approximately 15 minutes duration. Participants were invited to respond to each provided outcome using a 9-point Likert scale called the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Scale, whereby 1–3 = not important, 4–6 = important but not critical, 7–9 = critical, as well as an option to select if unable to score.[5] Consensus criterion were defined *a priori* as greater than or equal to 70% of responses rating the domain as "*critical*" (a score of 7–9) and less than or equal to 15% of responses rating the domain as "*not important*" (a score of 1–3).[5,12] This consensus definition has been used in previous studies and ensures it accounts for major disagreement in a minority group in an outcome that reaches apparent consensus.[10,12] Anonymity of participants was preserved throughout the Delphi study which commenced on 26 March 2024 and concluded on 6 May 2024.

Round 1

Participants were presented with a tabulated list of preliminary outcome measures and asked to grade each outcome using the 9-point GRADE scale. Participants were also provided with the opportunity to include their rationale for outcome scoring, to give feedback on the survey and to suggest any additional outcomes for inclusion. Additional outcomes and feedback were analysed by the study team.

Round 2

Following completion of the first round, outcomes were analysed to determine which outcomes met *a priori* criterion for consensus; these were removed from subsequent rounds. Participants were presented with the outcomes that had met consensus, a summary of feedback, percentage score distribution for each outcome and their own scores from Round 1. Outcomes that had not already achieved consensus were presented once again for voting, as were additional outcome measures suggested by participants in Round 1. Participants were again asked to rate each outcome using the 9-point GRADE scale and were given the option to maintain or amend their rating based on reflection on group results. Participants also had the opportunity to provide rationale and feedback.

Round 3

Data from Round 2 were analysed to identify additional outcomes meeting consensus criteria, and participants were informed of these at the start of Round 3. They were invited to re-score the remaining outcomes that had not reached consensus using the 9-point GRADE scale. Participants were able to see the anonymised distribution of responses from

the preceding round as well as the rating they had allocated each outcome in the preceding round.

Following participant feedback regarding a series of very similar outcomes relevant to abdominal and pelvis NSTI (colostomy, ileostomy, stoma, faecal diversion), and due to the concern that having too many highly similar options may potentially prevent any from meeting consensus even if conceptually the participants agreed, the primary investigating team determined to only carry forward the most inclusive of these terms; faecal diversion. All other outcomes that had not yet met consensus were included in Round 3 for a final round of ratings. On completion of Round 3, participants were asked to provide information on their clinical specialty where relevant and years of experience. All participants who completed Round 3 were asked if they wished to be acknowledged by name in the manuscript and offered the option to download a certificate of their involvement.

Consensus meeting

Following the completion and analysis of Round 3 data, a consensus meeting was held by the investigator team to finalise the COS. All preliminary outcomes meeting consensus were reviewed to remove or consolidate highly similar or interchangeable outcomes to determine the final list of outcomes for the NSTI COS.

STATISTICAL ANALYSIS AND CONSENSUS

Response rates were defined as the proportion of recruited panel members who completed each survey round. Survey responses for each outcome were summarised with descriptive statistics. Outcomes not reaching consensus were included in the analysis of the median rating and interquartile range for the ratings received in the final round. No statistical power calculations were performed for this study.

Results

PARTICIPANTS

The expert panel comprised of a total of 98 participants from 14 different countries, with 59 from South Asia, 21 from Oceania, 10 from Europe, five from North America, and one each from Southeast Asia, East Asia and Western Asia (Table 1). Low and middle income countries were represented in the study with 55 participants from India and two from Nepal.[14] Participants also identified their relevant stakeholder groups with 26 (27%) clinical researchers, 64 (65%) clinicians, 2 (2%) researchers and three (3%) NSTI survivors/caregivers. Three (3%) participants did not identify their stakeholder group. The panel consisted of experts from a diverse range of specialties: general surgery (28%), hyperbaric medicine (19%), anaesthesia (15%), intensive care (14%), emergency medicine (6%), internal medicine (5%), orthopaedic surgery (5%) (Table 1). The median professional experience level for clinicians and clinician researchers was 21 years (IQR 8–23) and 15 (6–25) respectively (Table 1). Fifty-six (57%) participants completed all three-rounds of the Delphi survey.

CORE OUTCOME SET

Fifty preliminary outcome measures were synthesised from the systematic review and presented across seven core areas: Mortality/Survival (n = 7), Physiological/Clinical (n = 11), Resource Use (n = 13), Life Impact (n = 4), Adverse Events (n = 3), Limb-specific outcomes (n = 4), Abdomen/Pelvis-specific outcomes (n = 8) (Table 2).

Round 1

Ninety-eight participants registered in the study, and 84 (86%) completed Round 1. (Figure 1). Ten participants commenced but did not complete Round 1. All outcomes voted on were included in the data analysis. Of the 50 preliminary outcome measures presented, ten outcomes from four core areas met *a priori* criteria for consensus during Round 1 and were removed from subsequent rounds; Mortality/Survival (n = 3), Resource Use (n = 2), Adverse Events (n = 3), Limb-specific outcomes (n = 2) (Table 3). No consensus outcomes were achieved for Life Impact, Physiological/Clinical and Abdomen/Pelvis-specific core areas. An additional 28 outcome measures were suggested by panel members for consideration. Co-investigators reviewed these suggestions, and of these nine outcomes were added to the list of outcomes provided in Round 2 (Figure 1). The remaining 40 outcomes from the preliminary set were retained for voting (Figure 1).

Round 2

Those who completed Round 1 were invited to participate in Round 2, and 58 (67%) of the 86 participants responded to the Round 2 survey (Figure 1). One participant commenced but did not complete Round 2, and all votes were included in analysis. Of the 49 outcome measures evaluated, an additional three outcomes reached consensus (Table 3). No outcome measures for life impact and abdomen/pelvis specific core areas reached consensus. After review of the outcome measures list and panel feedback, co-investigators decided to consolidate "*colostomy*", "*ileostomy required*" and "*stoma*" to the more inclusive term "*faecal diversion*". Forty-three outcomes were retained for Round 3.

Round 3

Among participants invited to Round 3, 56 (97%) of participants responded (Figure 1). Of the remaining 43 outcome measures rated in Round 3, two outcome measures from the Life Impact core area and one from Mortality/Survival met consensus criteria. Detailed scores and distribution for each outcome measure across each round including final consensus status are presented in Table 3.

Table 1

Characteristics of panel members; ^clinicians could select more than one specialty area to capture primary and secondary fields of practice; *information was collected only from participants that complete Round 3 of the Delphi study; IQR – interquartile range; NSTI – necrotising soft tissue infections

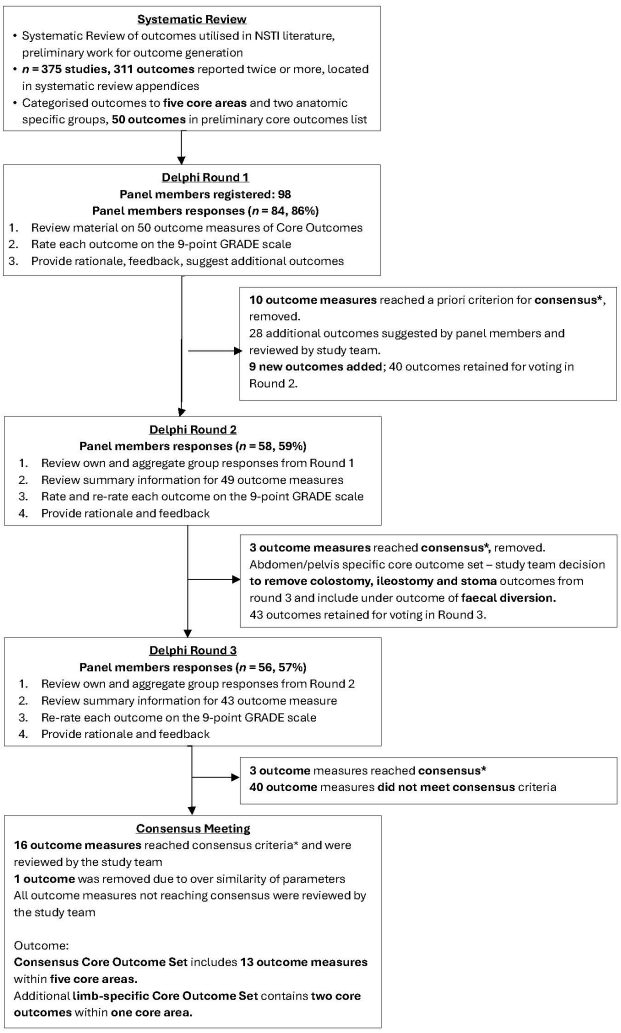
Characteristic	Round 1 (*n* = 98)	Round 2 (*n* = 59)	Round 3 (*n* = 56)
Country of practice, *n* (%)			
Australia	21 (21)	17 (29)	17 (30)
Belgium	1 (1)	1 (2)	1 (2)
Denmark	2 (2)	1 (2)	1 (2)
France	1 (1)	1 (2)	1 (2)
Germany	1 (1)	0	0
India	55 (55)	28 (47)	26 (46)
Ireland	1 (1)	0	0
Japan	1 (1)	1 (2)	1 (2)
Netherlands	2 (2)	2 (3)	2 (4)
Nepal	2 (2)	1 (2)	1 (2)
Oman	1 (1)	0	0
Singapore	1 (1)	1 (2)	0
Sweden	1 (1)	1 (2)	1 (2)
United Kingdom	1 (1)	1 (2)	1 (2)
USA	5 (5)	3 (5)	3 (5)
Other	2 (2)	1 (2)	1 (2)
Stakeholder, *n* (%)			
Clinician researchers	26 (27)	22 (37)	22 (39)
Clinician	64 (65)	33 (56)	30 (54)
Researcher	2 (2)	0	0
Consumer/NSTI survivor or caregiver	3 (3)	2 (3)	2 (4)
Other/not specified	3 (3)	2 (3)	2 (4)
Clinical specialty, *n* (%)^*			
Anaesthesiology			6 (15)
Emergency Medicine			3 (8)
General surgery			11 (28)
Hyperbaric medicine			8 (20)
Intensive care	Not collected		6 (15)
Internal medicine			2 (5)
Orthopaedic surgery			2 (5)
Paediatric anaesthesia			1 (3)
Paediatric surgery			1 (3)
Years of professional practice, median (IQR)*			15 (6–24)
Clinician researchers			15 (6–25)
Clinician			21 (8–23)

Table 2

Preliminary core outcome measures of necrotising soft tissue infections (core area, outcome domain, outcome measure) that were included in the study; outcome measures included as reported in systematic review by Wackett et al.[3]; outcome measures classified as per the COMET taxonomy recommended by Dodd et al.[9]; DAS-24 – Derriford Appearance Scale -24; ICU – intensive care unit; NICCE – Necrotising Infection Clinical Composite Endpoint; m-SOFA – modified Sequential Organ Failure Assessment score; SOFA score – Sequential Organ Failure Assessment score

Core area	Outcome domain	Outcome measure	Frequency reported in the literature
Death	Mortality/survival	Mortality without time specified	298
		In hospital mortality / 'survival to discharge'	94
		28-day mortality	20
		90-day mortality	19
		ICU mortality	13
		Mortality within 6 months / 180 days	12
		Mortality within 1 year	6
Physiological/ clinical	Musculoskeletal and connective tissue outcomes	Number of debridements required	151
		Number of procedures/surgeries required	86
	Skin and subcutaneous tissue outcomes	Skin graft required	88
		Surgical flap required	44
		Surgical reconstruction required	38
		Primary wound closure	22
		Wound healing time (cicatrisation time)	10
	Infection and infestation outcomes	SOFA score (Day 14)	4
		NICCE endpoint	3
		SOFA score (Day 28)	2
		m-SOFA (Day 14)	2
Life impact	Functioning	Medical outcomes Short Form-36	6
		Pain score (visual analogue scale)	2
	Emotional functioning/ wellbeing	Derriford appearance scale score	2
		DAS-24 questionnaire	1
Resource use	Hospital	Length of hospital stay	260
		Length of ICU stay (days)	103
		ICU-free days	7
		Ventilation (days)	33
		Ventilator-free days	9
		Days alive off life support at day 90	2
	Economic	Cost per patient	11
	Societal/carer burden	Discharged home	18
		Discharged to skilled nursing facility	9
		Discharged to rehabilitation	8
		Discharged to other hospital	6
		Days alive and out of hospital (by day 180)	6
		Discharged to hospice	3
Adverse events	Adverse events/effects	Septic shock	61
		Sepsis	46
		Organ failure / dysfunction	42
Limb-specific NSTI			
Physiological/ clinical	Musculoskeletal and connective tissue outcomes	Amputation performed	156
		Level of amputation	28
		Amputation during ICU stay	3
		Number of amputations	3
Abdomen/Pelvis-specific NSTI			
Physiological/ clinical	Gastrointestinal outcomes	Colostomy	75
		Faecal diversion	12
		Ileostomy required	5
		Stoma	5
	Renal and urinary outcomes	Suprapubic tube placement	21
		Cystostomy	34
	Reproductive system outcomes	Orchidectomy	46
		Penectomy	15

Figure 1
Flow diagram for modified Delphi consensus process; the *a priori* criteria for consensus were: ≥ 70% of responses rating the domain as 'critical' (a score of 7–9) and ≤ 15% of responses rating the domain as 'not important' (a score of 1–3); NSTI – necrotising soft tissue infection



By the end of the three-rounds of the Delphi survey, 16 outcome measures from five core areas and six domains had met consensus criteria; Mortality/Survival (n = 5), Physiological/Clinical (n = 1), Resource Use (n = 3), Life Impact (n = 2), Adverse Events (n = 3), Limb-specific outcomes (n = 2). No outcome measures reached consensus in the additional Abdomen/Pelvis-specific set.

Consensus review

At the final consensus meeting, outcomes of 28-day and 30-day mortality which had both met consensus criteria were considered too similar for both to be included in the core outcome set, and for pragmatic reasons, the investigator group decided to select one for recommendation only. Thirty -day mortality was the preferred choice after consideration of contemporaneous hospital and national administrative datasets.[15] Stakeholder ranking of 90-day mortality was reviewed; 39 (69.64%) stakeholders in Round 3 considered it to be critically important, and 1 (2%) considered it not important. Investigators agreed to accept that this met consensus criteria by rounding and recommend its inclusion in the COS. Consideration was also given to whether one of sepsis or septic shock should be removed and both were retained. The preliminary COS for NSTI is presented in Table 4.

Discussion

This COS is the recommendation of a minimum set of outcomes that should be reported in all studies for NSTI, however, it does not limit or prohibit the inclusion of other outcomes. NSTI can affect any anatomical region, each of which is likely to have outcomes of relevance to only that region. The study team set out to develop a core set of outcomes relevant to all categories of NSTI, with the addition of separate sub-sets to be collected for two of the most commonly affected anatomical regions; limb and abdomen/pelvis.[16,17] The aim in doing this was to identify outcomes considered critically important within each of these distinct anatomical sub-groups. Two outcome measures related to amputations reached consensus criteria in the Limb-specific core set, however, no consensus outcomes were reached in the Abdomen/Pelvis-specific core set. This may be attributed to the abundance of closely related outcomes, namely colostomy, stoma, ileostomy, and faecal diversion, that contributed to the lack of consensus amongst them. However, despite the decision to consolidate these outcomes into a single faecal diversion outcome after Round 2, it still did not meet consensus criteria, with only 43% of participants rating it as critically important with interquartile GRADE rating of 6–9 (Table 3). Potentially, faecal diversion may have been considered an intervention as opposed to an outcome measure in acute phase of perineal NSTI as a method to improve local wound treatment, with a definitive stoma requirement being considered the subsequent outcome.[18] The identification of an Abdomen/Pelvis-specific set of core NSTI outcomes remains a priority and should be further explored.

NSTIs have a significant life impact on patients.[14] Survivors have reported long-term physical, psychological and social consequences of NSTI which impact health-related quality of life and should be considered as part of the patient perspective in NSTI research.[14] Of the proposed ten outcome measures under the Life Impact core area in this study, only two reached consensus at the end of three rounds of voting; Medical Outcomes Short Form-36 (SF-36) and return to previous activities of daily living (ADLs).

The SF-36 is a 36-item health questionnaire developed in 1992 which assesses eight domains of health using scaled scores; physical functioning, role-physical functioning, bodily pain, general health, vitality, social function, role-

Table 3

Outcome measures (outcomes that did meet and did not meet consensus criteria + descriptive statistics); **a priori* criteria for consensus: ≥ 70% of responses rating the domain as 'critical' (a score of 7–9) and ≤ 15% of responses rating the domain as 'not important' (a score of 1–3); DAS-24 – Derriford Appearance Scale -24; EQ 5D – EuroQol 5 Dimension (quality of life measure); HAD scale – Hopsital Anxiety and Depression scale; ICU – intensive care unit; NICCE – Necrotising Infection Clinical Composite Endpoint; m-SOFA – modified Sequential Organ Failure Assessment score; PTSD – post traumatic stress disorder; SF36 – Short Form 36; SOFA score – Sequential Organ Failure Assessment score; VAS – visual analogue scale

Outcome measure by core area	Round 1				Round 2				Round 3				Decision*
	n votes	Score ≤ 3 *n* (%)	Score ≥ 7 *n* (%)	Median (IQR)	*n* votes	Score ≤ 3 *n* (%)	Score ≥ 7 *n* (%)	Median (IQR)	*n* votes	Score ≤ 3 *n* (%)	Score ≥ 7 *n* (%)	Median (IQR)	
Adverse events													
Organ failure/dysfunction	83	1 (1)	69 (83)	9 (7–9)									Consensus
Sepsis	83	1 (1)	68 (82)	8 (7–9)									Consensus
Septic shock	83	1 (1)	72 (87)	9 (7–9)									Consensus
Life impact													
Anxiety and depression at three months (HAD scale)					58	5 (9)	20 (34)	6 (4–7)	56	2 (4)	13 (23)	6 (5–6)	
DAS-24 questionnaire	78	10 (13)	34 (45)	9 (7–9)	54	7 (13)	23 (43)	6 (5–6)	52	6 (12)	13 (25)	6 (5–6.35)	
Derriford appearance scale score	75	6 (8)	25 (33)	6 (5–7)	52	4 (8)	11 (21)	6 (5–6)	50	3 (6)	9 (18)	6 (5–6)	
EQ5D-3L (at 30 days)					58	4 (7)	26 (45)	6 (5–7)	56	1 (2)	22 (39)	6 (5.75–7)	
EQ 5D-3L (at discharge)					58	4 (7)	17 (29)	6 (5–7)	56	3 (5)	12 (21)	6 (5–6)	
Medical Outcomes SF36	81	3 (4)	45 (56)	7 (6–8)	56	0	38 (68)	7 (6–7)	54	0	40 (74)	7 (6.25–7)	Consensus
Pain score (VAS)	85	5 (6)	45 (51)	7 (6–8)	58	2 (3)	23 (40)	6 (6-7)	56	2 (4)	13 (23)	6 (6–6)	
PTSD at three months (Impact of event scale)					57	4 (7)	16 (28)	6 (5–7)	55	1 (2)	10 (18)	6 (5–6)	
Return to previous activities of daily living					58	2 (3)	40 (69)	7 (6–8)	56	0	43 (77)	7 (7–8)	Consensus
EQ5D at three months					58	4 (7)	32 (55)	7 (5–8)	56	1 (2)	37 (66)	7 (6–7)	
Death													
28-day mortality	94	1 (1)	70 (74)	8 (6.3–9)									Consensus
30-day mortality					58	4 (7)	43 (74)	8 (6.25–9)					Consensus
90-day mortality	94	4 (4)	56 (60)	7 (6–8.8)	59	1 (2)	41 (69)	8 (6–9)	56	1 (2)	39 (70)	7 (6–7)	Consensus
ICU mortality	93	4 (4)	69 (72)	8 (6–9)									Consensus
In hospital mortality	94	0	75 (80)	8 (7–9)									Consensus
Mortality within one year	93	11 (12)	33 (35)	6 (4–7)	59	7 (12)	15 (25)	6 (4–6.5)	56	8 (14)	15 (27)	6 (5–7)	
Mortality within six months	94	11 (12)	44 (47)	6 (5–8)	59	5 (8)	20 (34)	6 (5–7)	56	6 (11)	15 (27)	5 (5–7)	

Table 3 continued.

Mortality without time specified	94	13 (14)	37 (39)	6 (4–8)	59	8 (14)	24 (41)	6 (3.5–7)	56	7 (13)	26 (46)	6 (3.75–7.25)	
Physiological / clinical													
m-SOFA (Day 14)	84	5 (6)	36 (43)	6 (5–8)	56	4 (7)	18 (32)	6 (5–7)	54	5 (9)	9 (17)	6 (5–6)	
NICCE endpoint	78	7 (9)	38 (49)	6 (5–8)	55	5 (9)	26 (47)	6 (6–8.5)	52	4 (8)	14 (27)	6 (5.8–7.3)	
Number of debridements	87	2 (2)	58 (67)	8 (6–9)	59	1 (2)	44 (75)	8 (6.5–9)					Consensus
Number of procedures/surgeries	87	2 (2)	55 (63)	7 (6-9)	59	2 (3)	36 (61)	8 (6–9)	56	3 (5)	32 (57)	8 (6–9)	
Primary wound closure	87	6 (7)	39 (45)	6 (5–8)	59	4 (7)	24 (41)	6 (5–7)	56	3 (5)	13 (23)	6 (5–6)	
Skin graft required	87	6 (7)	44 (51)	7 (5.5–8)	59	3 (5)	20 (34)	6 (5.5–7)	56	2 (4)	10 (18)	6 (6–6)	
SOFA score (Day 14)	87	7 (8)	47 (54)	7 (5–8)	59	7 (12)	28 (47)	6 (5–8)	56	6 (11)	17 (30)	6 (6–7)	
SOFA score (Day 28)	87	11 (13)	35 (40)	6 (5–7)	58	7 (12)	17 (29)	6 (5–7)	56	6 (11)	8 (14)	6 (5–6)	
Surgical flap required	87	7 (8)	43 (49)	6 (5–8)	59	4 (7)	19 (32)	6 (6–7)	56	2 (4)	11 (20)	6 (6–6)	
Surgical reconstruction required	87	4 (5)	55 (63)	7 (6–8)	59	2 (3)	36 (61)	7 (6–7)	56	2 (4)	35 (63)	7 (6–7)	
Wound healing time (cicatrisation time)	87	7 (8)	40 (46)	6 (5–8)	59	2 (3)	23 (39)	6 (5–8)	56	5 (9)	16 (29)	6 (5–7)	
Resource use													
Cost per patient	83	5 (6)	45 (54)	7 (6–8)	57	0	31 (54)	7 (6–9)	55	0	25 (45)	6 (6–9)	
Days alive and out of hospital (by day 180)	83	5 (6)	34 (41)	6 (5–8)	57	2 (4)	18 (32)	6 (5–7)	55	1 (2)	10 (18)	6 (5.5–6)	
Days alive off life support at day 90	83	8 (10)	33 (40)	6 (5–7)	57	3 (5)	20 (35)	6 (6–7)	55	2 (4)	12 (22)	6 (6–6)	
Discharge disposition					57	1 (2)	26 (46)	6 (6–7)	56	1 (2)	19 (34)	6 (5.75–7.25)	
Discharged home	84	4 (5)	53 (63)	7 (6–9)	58	0	44 (76)	8 (7–9)					Consensus
Discharged to hospice	83	6 (7)	32 (39)	6 (5–7)	58	4 (7)	13 (22)	6 (5.25–6)	56	0	8 (14)	6 (6–6)	
Discharged to other hospital	84	3 (4)	32 (38)	6 (5–7)	58	4 (7)	11 (19)	6 (5–6)	56	2 (4)	6 (11)	6 (5–6)	
Discharged to rehabilitation	84	4 (5)	33 (39)	6 (5–7.25)	58	2 (3)	16 (28)	6 (5–7)	56	2 (4)	11 (20)	6 (6–6)	
Discharged to skilled nursing facility	84	4 (5)	30 (36)	6 (5–7.25)	58	3 (5)	16 (28)	6 (5–7)	56	4 (7)	10 (18)	6 (6–6)	
ICU-free days	84	3 (4)	40 (48)	6 (5–7.25)	58	3 (5)	22 (38)	6 (6–7)	56	2 (4)	18 (32)	6 (6–7)	
Length of hospital stay	84	0	65 (77)	8 (7–9)									Consensus
Length of ICU stay (days)	84	0	69 (82)	8 (7–9)									Consensus
Ventilation (days)	84	3 (4)	51 (61)	7 (6–9)	58	2 (3)	37 (64)	7 (6–9)	56	2 (4)	37 (66)	8 (6–9)	
Ventilator-free days	84	4 (5)	35 (42)	6 (5–7)	58	3 (5)	18 (31)	6 (5–7)	56	1 (2)	17 (30)	6 (6–7)	
Limb-specific													
Amputation during ICU stay	81	8 (10)	40 (49)	6 (5–8)	56	4 (7)	25 (45)	6 (5.75–9)	54	5 (9)	27 (50)	6.5 (6–9)	

Table 3 continued.

															Consensus
Amputation performed	81	0	72 (89)	9 (8–9)											Consensus
Level of amputation	81	0	60 (74)	8 (6–9)											
Number of amputations	80	3 (4)	48 (60)	7 (6–9)	56	2 (4)	32 (57)	7 (6–9)	54	2 (4)	32 (59)	8 (6–9)			
Return to full function of affected limb					56	1 (2)	33 (59)	7 (6–8)	54	2 (4)	32 (59)	7 (6–7)			
Trunk-specific															
Colostomy	81	2 (2)	54 (64)	7 (6–9)	56	1 (2)	31 (55)	7.5 (6–8)							
Cystostomy	81	2 (2)	38 (47)	6 (5–8)	56	1 (2)	22 (39)	6 (5–8)	54	1 (2)	16 (30)	6 (5–7)			
Faecal diversion	81	0	45 (56)	7 (6–8)	56	0	28 (50)	6.5 (6–9)	54	0	23 (43)	6 (6–9)			
Ileostomy required	81	3 (4)	45 (53)	7 (6–9)	56	1 (2)	22 (39)	6 (5–8)							
Orchidectomy	81	1 (1)	44 (54)	7 (6–8)	56	1 (2)	31 (55)	7 (6–8)	54	1 (2)	24 (44)	6 (6–8)			
Penectomy	79	3 (4)	42 (53)	7 (6–8)	56	1 (2)	25 (45)	6 (6–8)	54	1 (2)	20 (37)	6 (6–8)			
Stoma	80	3 (4)	49 (61)	7 (6–9)	56	0	31 (55)	7 (6–9)							
Suprapubic tube placement	80	6 (8)	28 (35)	6 (5–7)	56	2 (4)	13 (23)	6 (5–6)	54	2 (4)	11 (20)	6 (5–6)			

emotional functioning and mental health.[19] Component analysis of survey results can also generate two summary scales of health; a Physical Component Score and a Mental Component Score.[20]

Health related quality of life outcomes, such as SF-36, are commonly incorporated into randomised controlled trials to consider patient specific outcomes of various conditions, however there are several challenges with its use. The results of SF-36 in several studies do not necessarily modify the interpretation of trial results even when discordant from primary efficacy outcomes, suggesting the need for standardised interpretation of patient outcomes.[21] Developed as a generic, multipurpose tool, the SF-36 has been shown to not capture the extent of profound psychological impacts, notably observed in NSTI survivors, compared to more targeted assessment tools such as the Hospital Anxiety and Depression Scale (HADS) and Impact of Events Scale (IES).[22] This suggests the potential need for an additional measure to detect the psychosocial impact of NSTI. HAD and IES were both proposed as outcomes as part of the Delphi survey after Round 1 but did not achieve consensus. Given the high sensitivity of the IES for mental health, the performance of IES in a yet unpublished systematic review of patient reported outcome measures in NSTI, and the profound psychological impact NSTI has on survivors, the authors suggest that IES may be a valuable tool to evaluate the psychological impact of NSTI.[22]

Once patients have survived NSTI, return to function emerges as a critical patient-specific outcome. Return to previous ADLs was proposed by a panel member at completion of Round 1 and subsequently included in Round 2 of the survey. The term ADL can be further subdivided into basic/personal ADLs and instrumental/extended ADLs, however universal agreement and consensus of what is recorded, scoring scale, quantifying functional limitation and the time frame of capture is unclear and can be problematic, and requires further study.

In considering the core area of resource use, panel members were provided with several discharge destination outcomes including discharge disposition, discharged home, discharged to hospice, discharged to other hospital, discharged to rehabilitation and discharged to skilled nursing facility. Of these, discharge home was the only outcome to meet consensus criteria with 76% rating it as critically important. All other discharge disposition related outcomes were predominantly rated between important and critically important (interquartile GRADE rating 5–7) (Table 3). This suggests a general agreement across the stakeholder groups of the importance for patients that have survived NSTI to ultimately be able to return home. Predicators of discharge disposition to other settings include patient factors such as age, gender and comorbidities, complications such as amputations and sepsis, complex care and persistent functional deficits, where patients would require ongoing rehabilitation or services.[23] Discharge disposition to

Table 4

Core outcome set; outcome measures reaching *a priori* consensus criteria classified as per the COMET taxonomy recommended by Dodd et al.[9]; the *a priori* criteria for consensus were : ≥ 70% of responses rating the domain as 'critical' (a score of 7–9) and ≤ 15% of responses rating the domain as 'not important' (a score of 1–3); ICU – intensive care unit

Core area	Outcome domain	Outcome measure
Death	Mortality/survival	In hospital mortality
		30-day mortality
		90-day mortality
		ICU mortality
Physiological/clinical	Musculoskeletal and connective tissue outcomes	Number of debridements required
Life impact	Functioning	Medical Outcomes Short Form-36 (SF36)
		Return to previous activities of daily living
Resource use	Hospital	Length of hospital stay
		Length of ICU stay (days)
	Societal / carer burden	Discharged home
Adverse events	Adverse events/effects	Septic shock
		Sepsis
		Organ failure/dysfunction
Limb-specific NSTI		
Physiological/clinical	Musculoskeletal and connective tissue outcomes	Amputation performed
		Level of amputation

non-home destinations is also indicative of poorer patient outcomes and has been associated with greater 30-day mortality and functional limitation.[24]

The most consistently important outcomes to the participants with lived experience of NSTI or caregivers were: SF-36, a simple quality of life assessment EQ-5D at 30 days, and 90-day mortality, indicating that what these stakeholders value most is quality of life and survival beyond the acute phase of NSTI.

There are several limitations to this paper. The COS developed in this study reflects the expert opinion on the topic, and therefore may be prone to bias of the participants involved. However, we endeavoured to minimise this potential bias by involving a large number of multinational stakeholders with diverse expertise in NSTI. Although thirteen outcomes comprise the determined COS for all NSTI, with two additional outcomes forming the Limb-specific COS, no outcomes reached consensus for the Abdomen/Pelvis-specific COS. This lack of abdomen/pelvis related core outcomes could result in increased heterogeneity in comparing outcomes of NSTI involving the abdomen, groin and perineum. Further work to develop an additional COS specific to abdominal/pelvis NSTI should be considered. Variability exists in the granularity of the outcomes chosen, from broad concepts (return to previous ADLs) to the use of a specific tool (SF-36) for assessing life impact. Mortality outcomes that met consensus have determined time-points (30- and 90-days), while other outcomes do not. Outcomes without specified time points may not adequately reduce the heterogeneity of data collected for meta-analysis, and future work should clarify recommended time points for collection of these data.[25] Although approximately one third of participants who completed all rounds of the Delphi were surgical specialists (general, orthopaedic and paediatric surgery) an absence of urologists and plastic surgeons and limited orthopaedic representation (5%) in the panel may have impacted the outcomes considered important in the additional anatomical and intervention sets.

Response rates between Round 1 and 2 of the Delphi dropped from 86% to 59% of those who had registered to participate, with an overall response rate of 57% by Round 3. While there is no formal guidance around sample size and acceptable response rate, several study design factors can increase the potential for attrition bias, which can contribute to a false sense of consensus in remaining participants leading to a response bias.[5] In this study, we initially recruited a large sample size of 98 participants across demographically and geographically diverse populations and expected a degree of attrition from the sample (Table 1). Limiting the preliminary list of outcomes and length of Delphi survey was also to minimise participant burden each round. Only those who had completed each round were invited to the subsequent round. Reminder emails were sent during the rounds to encourage response rates. However, despite the attrition rate, the distribution of clinicians to clinician researchers, NSTI

survivors and caregivers, and country of practice remained relatively consistent across all three rounds (Table 1), indicating that the results of the study remain representative of the stakeholder groups.

Finally, there are potential challenges relating to the development of COS and barriers to uptake in future studies. The lack of validated measurement instruments for certain core outcomes such as return to previous ADLs and organ failure/dysfunction increases the difficulty in determining what and how to measure and acts as a barrier to applying the COS.[26] Establishment of core measure instruments that have appropriate psychometric analysis and assessment for feasibility, validity and responsiveness would improve the COS.[10] Similarly, optimal timepoints for outcome assessments of functional limitation are yet to be established. A minimum set of timepoints (i.e. at discharge, three, six and 12 months) would ensure homogeneity of data and cross-study comparison whilst additional timepoints could be considered to better understand the trajectory of management and recovery, however many centres may not be adequately resourced to collect this data. Whilst the authors encourage collection of data at time points up to and even beyond 12 months, this has not been proposed in this minimum dataset. Therefore, development of a core measurement instrument set is an urgent priority to optimise the applicability and uptake of the COS for NSTI.

Because of the absence of consensus amongst NSTI experts regarding the utility of HBOT, NSTI treatment guidelines are inconsistent, and patients receive inequitable care locally and internationally.[6,8] The rarity of NSTI and of HBOT centres with critical care capabilities make it extremely challenging to perform adequately powered controlled studies of adequate scale. The development and consistent uptake of this COS for NSTI is anticipated to improve the quality of evidence to support or refute the role of HBOT (and other interventions) for NSTI, by providing more homogenous outcome reporting and increasing the data available for subsequent meta-analysis. Use of the COS in future trials can also provide researchers with assurance that they have selected outcomes determined to be critical by a large, multinational and multidisciplinary group of NSTI experts.

Conclusions

Using a three-round modified Delphi process, consensus on the content of an NSTI minimum outcome set was achieved. The COS developed through this process contains 13 outcomes from the following five core areas; Mortality/Survival (in-hospital mortality, 30 day mortality, 90-day mortality, ICU mortality), Physiological/Clinical (number of debridements), Life Impact (medical outcomes short form-36, return to previous activities of daily living), Resource Use (length of hospital stay, length of ICU stay, discharged home), Adverse Events (septic shock, sepsis, organ failure/dysfunction). Within the Limb-specific subset of outcomes, two additional outcomes met consensus within the Physiological/Clinical core area (amputation performed, level of amputation). Having developed a preliminary COS for NSTI using robust consensus methods, we encourage researchers to include these outcomes in future studies.

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