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Beating the Empty Pelvis Syndrome: The PelvEx Collaborative Core Outcome Set Study Protocol

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Abstract:

Introduction:

The empty pelvis syndrome is a significant source of morbidity following pelvic exenteration surgery. It remains poorly defined with research in this field being heterogenous and of low quality. Furthermore, there has been minimal engagement with patient representatives following pelvic exenteration with respect to the empty pelvic syndrome. "PelvEx – Beating the empty pelvis syndrome" aims to engage both patient representatives and healthcare professionals to achieve an international consensus on a core outcome set, pathophysiology, and mitigation of the empty pelvis syndrome.

Methods and analysis:

A modified-Delphi approach will be followed with a three-stage study design. Firstly, statements will be longlisted using a recent systematic review, healthcare professional event, patient and public engagement, and Delphi piloting. Secondly, statements will be shortlisted using up to three rounds of online modified-Delphi. Thirdly, statements will be confirmed and instruments for measurable statements selected using a virtual patient-representative consensus meeting, and finally a face-to-face healthcare professional consensus meeting.

Ethics and dissemination:

The University of Southampton Faculty of Medicine ethics committee has approved this protocol, which is registered as a study with the Core Outcome Measures in Effectiveness Trials Initiative. Publication of this study will increase the potential for comparative research to further understanding and prevention of the empty pelvis syndrome.

ClinicalTrials.gov registration number: NCT05683795

Strengths and limitations (up to 5 bullet points needed):

- This study will not produce new evidence on the empty pelvis syndrome. As with any Delphi study it is a heuristic device relying on expert knowledge to co-construct knowledge and recommendations. It is only as good as the available evidence and the participating experts.
- The empty pelvis syndrome is a research priority for patients undergoing pelvic exenteration, with poor evidence to support management strategies and prevention. A consensus study on this topic will facilitate generation of higher quality evidence in the form of a meta-analyses.
- The study is supported by the PelvEx Collaborative who will be in a position to immediately utilise results and momentum from this consensus study to undertake an international observational study on the empty pelvis syndrome.
- This study has been designed in the UK with chiefly UK-based patient advocacy groups. Recruitment of international non-English speakers may be challenging.

Introduction:

Pelvic exenteration encompasses radical, multi-visceral surgery for locally advanced primary and locally recurrent pelvic malignancies. It is hypothesised that the empty space created following pelvic exenteration can result in a sequelae of complications such as infected pelvic collections, prolonged ileus, mechanical bowel obstruction, perineal sinus, and entero-perineal fistula. This pathological process has been termed, "the empty pelvis syndrome" (EPS). Morbidity relating to EPS is estimated to be responsible for up to 40% of complications following pelvic exenteration (1).

EPS was first defined in 1993 by Barber et al, as "*A flulike illness with malaise, elevated temperature, and increased discharge from the perineal sinus that may continue for many years, particularly among those undergoing heavy irradiation* (2). The same condition has also

been labelled as 'the empty pelvic syndrome' or 'pelvic burn syndrome' (3). There is presently renewed interest in EPS, with five publications making reference to it between 1993 – 2014 (2, 4-7), and twenty-four papers between 2015 – 2022 (1, 3, 8-29). These citations give inconsistent definitions and outcomes for EPS. As a result, there is limited scope for meta-analyses that may help guide prevention and management of this syndrome. A recent systematic review on reconstructive techniques for EPS cited low quality evidence with small patient numbers, precluding the ability to provide evidence-based recommendations as to the most appropriate reconstructive technique (1).

The anatomical and pathophysiological mechanisms behind EPS are largely undefined. Major bone or nerve resections have been shown to result in surgical intervention for complications related to EPS. These factors may be surrogate markers for more extensive surgery (25). In recent years, more radical pelvic exenterations are being performed along with the addition of intra-operative oncological strategies like intra-operative radiotherapy, in an attempt to improve oncological outcomes for patients (19, 30). The degree of morbidity and the number of patients affected by EPS are therefore likely to increase. The formulation of a consensus definition for EPS, with a measurable core outcome and core descriptor set would limit heterogeneity of data reporting, enhancing the quality of the evidence base, with the aim of improving outcomes for patients undergoing pelvic exenteration.

Patients are key stakeholders in this process, however, to date they have not had an active role in design and participation in any research on EPS. The UK National Cancer Research Institute and James Lind Alliance partnership have defined the Living With and Beyond Cancer Top 10 Priorities, and this study dovetails with several of these priorities (31):

- The consequences of EPS can be implicated in the persistent late effects of cancer treatments.
- Patients eligible for pelvic exenteration have complex needs with often several surgical and oncological teams involved in their care
- The psychological impact of EPS is under-reported with no data captured in this area.
- The pathophysiology of EPS currently is poorly understood; and addressing this will lead to improved treatments.

- A defined core outcome set, and core descriptor set will enable better prediction of which patients are at risk of developing EPS post-surgery.

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched on 14/07/2022 and there were no references to pelvic exenteration, complex pelvic cancer, or EPS. A three-stage study design using healthcare professionals and patient representatives as stakeholders will be followed:

1. Longlisting statements through systematic review, healthcare professional event, patient and public engagement (PPI) and piloting
2. Shortlisting statements using up to three rounds of online modified-Delphi
3. Confirming statements with a patient-representative virtual consensus meeting, and a face-to-face healthcare professional consensus meeting

Aims and objectives:

The primary aim of this study is to define a measurable core outcome set for EPS involving both healthcare professionals and patient representatives as stakeholders.

Secondary aims include:

- Establishing consensus on the pathophysiology of EPS with a view to forming a written definition and a measurable core descriptor set.
- Exploration of consensus on the reconstructive techniques that can be used to mitigate the effects of EPS.

Methods and analysis:

This study has been designed in accordance with Guidance on Conducting and REporting DElphi Studies (CREDES), the COMET handbook, Consensus-based Standards for the selection of health Measurement Instruments (COSMIN)/COMET guidance, Core Outcome Set-STAndardised Protocol Items (COS-STAP) statement, and Core Outcome Set-STAandards for Reporting (COS-STAR) Guidelines (32-36). It has been registered on the COMET database (37) and ClinicalTrials.gov (NCT05683795).

Patient and public involvement (PPI):

Patients are essential stakeholders, therefore PPI using local networks was established during the design stage of the study with patient representatives joining the project steering committee. Further PPI engagement was established by involving the Bowel Research UK People and Research Together (BRUK PaRT) programme, CommunitiesFirst, and World Federation of Incontinence and Pelvic Problems. This ensured patient facing study materials were appropriate, and that patient representatives contributed directly to creating the longlist of statements. Patients will be invited to participate in the study utilising these networks, with BRUK PaRT also advertising the study for patient representatives through social media.

Stakeholders:

The PelvEx Collaborative is a diverse international group of healthcare professionals from 140 hospitals across five continents that provide pelvic exenteration services. The PelvEx Collaborative have previously undertaken Delphi studies; therefore, this is an ideal, motivated and logistically convenient platform to undertake a Delphi study due to its expertise, access to patients as key stakeholders, and the opportunity to undertake a face-to-face consensus meeting at the PelvEx Collaborative annual scientific meeting. (38, 39).

In a Delphi study there is no agreement on how a group of experts should be selected, and there is no need for a statistically representative sample to be obtained (40). Therefore, all members of the PelvEx Collaborative will be invited to be involved in the study, generating, multi-professional, multi-national representation. Members of the PelvEx Collaborative will also be encouraged to engage their individual institutional PPI networks to participate in the project.

Stage 1 – creating an EPS statements longlist:

Statements were divided into three domains:

1. An EPS core outcome set
2. Pathophysiology of EPS
3. Mitigation of EPS

A recent systematic review and subsequently published literature on EPS were searched for statements in keeping with these domains (1, 25, 26). The PelvEx Collaborative held an international face-to-face meeting in Amsterdam in 2022 where an empty pelvis initiative was presented, and further statements were generated based on formal and informal discussions at this meeting. The study steering committee was then formed from an international group of nine healthcare professionals, three patient representatives that had undergone pelvic exenteration, and PPI professionals from BRUK PaRT – further statements were then generated from opinions of this committee.

The study is sponsored by the University of Southampton who provide institutional access to the Qualtrics Survey platform. A pilot of the first Delphi round was produced based on the statements generated above and trialled with the study steering committee. This included open questions to generate further statements. The time taken for individuals to complete the pilot study was also timed to allow an approximation of the burden of time required by participants to be included in invitation letters. Following piloting, the study steering committee met to confirm the longlist of 70 statements for the first Delphi round, the number of statements for each domain was as follows:

1. An EPS core outcome set – 19 statements
2. Pathophysiology of EPS – 17 statements
3. Mitigation of the EPS – 34 statements

It was decided that patient representatives would only be invited to participate in the core outcome set domain, as it was felt they would be unlikely to have the experience in the other domains to provide helpful input into forming consensus. Statements in the core outcome set domain will therefore be presented in lay terms with technical language following this in parentheses.

Stage 2 – creating an EPS statement shortlist:

Three Delphi rounds are likely to be required with two separate stakeholder groups taking part: patient representatives and healthcare professionals. Members of the PelvEx Collaborative are experts in providing pelvic exenteration with experience of EPS, the healthcare professional stakeholder group will be recruited by contacting this group. The

inclusion criteria for patient representatives is any individual that has undergone pelvic exenteration, which is defined as surgery to remove multiple organs from the pelvis, including beyond total mesorectal excision plane operations. This will include patients with any cancer (i.e., primary or recurrent colorectal, gynaecological, urological and connective tissue malignancies). Patient representatives will be sought through BRUK PaRT, CommunitiesFirst, World Federation of Incontinence and Pelvic Problems, and by encouraging members of the PelvEx Collaborative to approach their individual institutional PPI networks. Patient representatives that do not speak English are also eligible to participate with translation of patient facing materials to be provided by LanguageInsight, and healthcare professionals from the PelvEx Collaborative able to appropriately translate information. In order to be able to describe the diversity of the stakeholder groups demographic information will be sought in the first Delphi round.

Potential participants will be emailed invitation letters along with a link to the Qualtrics first Delphi round. Before voting on statements Qualtrics will present participants with an informed consent form that must be completed first. Qualtrics will utilise the 'Force Response' function, therefore participants must complete all of a Delphi round before being able to submit. This will eliminate missing data from the study.

The first Delphi round will include all longlisted statements generated from stage 1 arranged in alphabetic order to reduce leading questions or researcher bias. These will be scored by participants from 1 – 9 on a Likert scale, as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (41). With 1 – 3 representing 'not important', 4 – 6 representing 'important but not critical' and 7 – 9 representing 'critical for inclusion.' A score of '0' will also be included, which will mean 'unable to comment.' The final questions on each domain will be open in order to avoid early closure of ideas among participants, so that further insight not anticipated in stage 1 of the process is gathered with the intention to generate new statements for the second round of the Delphi.

There is no recognised formal way of defining consensus in Delphi studies, however it is specified here *a priori* that in order for statements to progress they must obtain stricter

consensus between subsequent rounds. To progress from the first round to the second-round statements must be rated 7 – 9 by 50% or more of participants, and by 1 – 3 by no more than 15% of participants in at least one stakeholder group. Beyond round 2 retained items must be rated between 7 – 9 by over 70% of respondents, and by 1 – 3 by less than 15% by at least one stakeholder group. This method reduces the chance of dropping statements that may have been rated more highly in subsequent rounds once participants have received feedback. From piloting there was concern that a large proportion of statements for the core outcome set were rated as essential, therefore it was decided *a priori* that if there are 10 or more core outcome set statements reaching consensus by the end of a second round then a third Delphi round will take place, with higher level consensus required, defined as 95% participants voting 7 – 9 that the statement should be included. This approach is based on previous core outcome set studies (42, 43).

Responses to open questions from the first round will undergo thematic analysis and will be used to formulate new statements for addition to subsequent rounds. Any comments that apply to particular statements, which are not able to be formulated into new statements will be presented verbatim in subsequent rounds alongside relevant statements. Open questions will not be included from the second round.

It is anticipated that each round will be open for one month with personalised email reminders issued to participants at 2 weeks and 48 hours from the deadline to encourage responses. Any participants wishing to drop out will be asked to give a reason for doing so, to facilitate recognition of any systematic attrition bias. Only individuals that completed the previous round will be contacted to take part in a subsequent round; if attrition leads to participation dripping below 70% of a previous round, the Delphi study will be terminated as below this level, rigor cannot be guaranteed. The study would then proceed directly to stage 3.

Analysis for patient representatives and healthcare professionals between rounds will take place separately. It is anticipated that more healthcare professionals will participate, therefore analysis of these two groups together would potentially reduce the importance given to the patient voice. There will be presentation of this separate analysis for subsequent

rounds using medians and interquartile ranges, with how individuals voted in a previous round also disseminated. Histograms will also be included to facilitate understanding for patient representatives unfamiliar with descriptive statistics.

If progression of the Delphi rounds deviates from the presented protocol, decisions on whether to stop or continue to the Delphi will be taken by the Delphi steering committee.

Stage 3 – finalising EPS statements:

Any statements reaching consensus by the end of stage 2 that are measurable will have options for instruments prepared in accordance with COSMIN/COMET guidance (34). All potential instruments for measurement will be selected using the opinion of the study steering committee and reviews of the relevant literature, which will include instrument feasibility assessments. These options will then be presented at consensus meetings.

PelvEx 2023 is the international meeting of the PelvEx Collaborative and would be an ideal time to hold a face-to-face consensus meeting for participating healthcare professionals. It was felt this meeting would not be appropriate for patient representatives as it will involve significant travel, patients may be heavily influenced by the opinions of healthcare professionals and may not feel as able to voice their opinions in front of a large audience.

To increase the number of involved patient representatives a virtual consensus meeting for patient representatives will be held prior to PelvEx 2023, which will be supported by BRUK PaRT. Participants will be sent results from the final round of the Delphi including their individual final votes. Any non-English speaking patient representatives will also be invited to participate with an appropriate multi-lingual healthcare professional from the PelvEx Collaborative joining the meeting to allow translation. At the start of the meeting demographic information will be requested to allow reporting of diversity. Any statements retained from the final Delphi round for the core outcome set will be included and participants will be asked to anonymously vote on whether the statement should stay in, be removed, or whether they are unsure. Where there is no consensus or participants are unsure, then further discussion will take place with an effort to capture dissenting views to determine the nature of a polarised response, also considering whether statements overlap

and can be combined. Further voting will take place, followed by further discussion; if there is persistent disagreement a final round of voting will take place using a majority rule.

For the core outcome set statements felt to be important, possible instruments to measure these statements will be presented for approval. It is anticipated that selection of instruments for patients will be difficult as the evidence on their methodology is likely to be challenging to understand, however it is hoped that with support from research facilitators that patients will be able to judge relevance, comprehensiveness and comprehensibility of the available instruments. This meeting will be recorded for analysis and potential presentation of patients speaking at PelvEx 2023 to help healthcare professionals understand patient experience.

Prior to PelvEx 2023 the results of the final Delphi rounds, statements for voting, and the patient virtual consensus meeting will be sent out to participants, including how individuals that participated voted in the final Delphi round. A list of delegates at PelvEx 2023 will be obtained along with demographic information, and whether or not they were involved in stage 2 of the project. Anonymous voting will be across all three domains and will follow the same pattern as the patient representative meeting.

Measurable statements that are included will have their pre-determined instruments presented for voting. If there is only one possible feasible instrument then participants will be permitted to vote either for this instrument, or that a recommendation is made for development of new instruments or that additional validation studies are required. It is difficult to predict how many statements will be voted upon and discussed. A further round of online voting or virtual consensus meetings following PelvEx 2023 may be required. This will be at the discretion of the study steering committee.

By the end of stage 3 the following should have been achieved for each domain:

1. A measurable core outcome set for EPS
2. Statements on pathophysiology of EPS generating a measurable core descriptor set and contributing to a written definition of EPS

3. To have established where there is consensus on current reconstructive techniques used to mitigate EPS, which will be graded by strength of recommendation and level of evidence (44).

It is unclear what the anatomical and pathophysiological causes of EPS are, how it can be prevented, and how its sequelae can be measured. EPS can be life-threatening and its consequences difficult to manage. This represents an ongoing, urgent, unmet clinical and research need in this growing patient population.

Ethics and dissemination:

Ethical approval for this protocol has been given from the University of Southampton under the ERGO II reference number 77306.

Any deviations from this protocol will be described and justified. Once stage 3 of the project is completed the project will be reviewed by an external board prior to publication and dissemination. This will be paper by the PelvEx Collaborative as per previous work, with utilisation of CRedIT taxonomy to encourage collaborators to engage with the process (38, 39, 45). Publication will be in peer reviewed journals and dissemination through professional collaborators and associated networks to ensure international adoption. In addition, the patient advocacy groups involved will also assist in dissemination of the research.

Funding:

The study coordinator, Mr Charles West, is a PhD candidate at University of Southampton and has received charitable funding from Bowel Research UK to run this study. He is also sponsored by Penguins Against Cancer and PLANETS Cancer Charity.

Contributors:

This protocol is written on behalf of the PelvEx Collaborative, listed below. CW, MW, AM, ID, TG, PS, JT, CB, GG, NW, SA, SC, and SR formed the study steering committee.

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West CT, West MA, Mirnezami AH, Drami I, Glyn T, Sutton PA, Tiernan J, Behrenbruch C, Guerra G, Woodward N, Applin S, Charles SJ, Rose SA, Aalbers AGJ, Abdul Aziz N, Abecasis N, Abraham-Nordling M, Akiyoshi T, Alahmadi R, Alberda W, Albert M, Andric M, Angeles M,

Angenete E, Antoniou A, Armitage J, Auer R, Austin KK, Aytac E, Aziz O, Bacalbasa N, Baker RP, Bali M, Baransi S, Baseckas G, Bebington B, Bedford M, Bednarski BK, Beets GL, Berg PL, Bergzoll C, Beynon J, Biondo S, Boyle K, Bordeianou L, Brecelj E, Bremers AB, Brown K, Brunner M, Buchwald P, Bui A, Burgess A, Burger JWA, Burling D, Burns E, Campain N, Carvalhal S, Castro L, Caycedo-Marulanda A, Ceelen W, Chan KKL, Chang GJ, Chew MH, Chok AK, Chong P, Christensen HK, Clouston H, Collins D, Colquhoun AJ, Constantinides J, Corr A, Coscia M, Cosimelli M, Cotsoglou C, Coyne PE, Creavin B, Croner RS, Damjanovic L, Daniels IR, Davies M, Davies RJ, Delaney CP, de Wilt JHW, Denost QD, Deutsch C, Dietz D, Domingo S, Dozois EJ, Drozdov E, Duff M, Egger E, Eglinton T, Enrique-Navascues JM, Espín-Basany E, Evans MD, Eyjólfsdóttir B, Fahy M, Fearnhead NS, Fichtner-Feigl S, Flatmark K, Fleming F, Flor B, Folkesson J, Foskett K, Frizelle FA, Funder J, Gallego MA, García-Granero E, García-Sabrido JL, Gargiulo M, Gava VG, Gentilini L, George ML, George V, Georgiou P, Ghosh A, Ghouti L, Gil-Moreno A, Giner F, Ginther N, Glover T, Goffredo P, Golda T, Gomez CM, Griffiths B, Gwenaël F, Harris C, Harris DA, Hagemans JAW, Hanchanale V, Harji DP, Helbren C, Helewa RM, Hellawell G, Heriot AG, Hochman D, Hohenberger W, Holm T, Holmström A, Hompes R, Hornung B, Hurton S, Hyun E, Ito M, Iversen LH, Jenkins JT, Jourand K, Kaffenberger S, Kandaswamy GV, Kapur S, Kanemitsu Y, Kaufman M, Kazi M, Kelley SR, Keller DS, Kelly ME, Kersting S, Ketelaers SHJ, Khan MS, Khaw J, Kim H, Kim HJ, Kiran R, Koh CE, Kok NFM, Kokelaar R, Kontovounisios C, Kose F, Koutra M, Kraft M, Kristensen HØ, Kumar S, Kusters M, Lago V, Lakkis Z, Lampe B, Langheinrich MC, Larach T, Larkin J, Larsen SG, Larson DW, Law WL, Laurberg S, Lee PJ, Limbert M, Loria A, Lydrup ML, Lyons A, Lynch AC, Mackintosh M, Mann C, Mantyh C, Mathis KL, Margues CFS, Martinez A, Martling A, Meijerink WJHJ, Merchea A, Merkel S, Mehta AM, Mehigan B, McArthur DR, McCormick JJ, McCormick P, McDermott FD, McGrath JS, McPhee A, Maciel J, Malde S, Manfredelli S, Mikalauskas S, Modest D, Monson JRT, Morton JR, Mullaney TG, Navarro AS, Neeff H, Negoi I, Neto JWM, Nguyen B, Nielsen MB, Nieuwenhuijzen GAP, Nilsson PJ, Nordkamp S, O'Dwyer ST, Paarnio K, Palmer G, Pappou E, Park J, Patsouras D, Peacock A, Pellino G, Peterson AC, Pfeffer F, Piqeur F, Pinson J, Poggioli G, Proud D, Quinn M, Oliver A, Quyn A, Radwan RW, Rajendran N, Rao C, Rasheed S, Rasmussen PC, Rausa E, Regenbogen SE, Reims HM, Renehan A, Rintala J, Rocha R, Rochester M, Rohila J, Rothbarth J, Rottoli M, Roxburgh C, Rutten HJT, Ryan ÉJ, Safar B, Sagar PM, Sahai A, Saklani A, Sammour T, Sayyed R, Schizas AMP, Schwarzkopf E, Scripcariu D, Scripcariu V, Seifert G, Selvasekar C, Shaban M, Shaikh I, Shida D, Simpson A, Skeie-Jensen T, Smart NJ,

Smart P, Smith JJ, Smith T, Solbakken AM, Solomon MJ, Sørensen MM, Spasojevic M, Steele SR, Steffens D, Stitzenberg K, Stocchi L, Stylianides NA, Swartling T, Sumrien H, Swartking T, Takala H, Tan EJ, Taylor C, Taylor D, Tejedor P, Tekin A, Tekkis PP, Teras J, Thanapal MR, Thaysen HV, Thorgersen E, Thurairaja R, Toh EL, Tsarkov P, Tolenaar J, Tsukada Y, Tsukamoto S, Tuech JJ, Turner G, Turner WH, Tuynman JB, Valente M, van Ramshorst GH, van Rees J, van Zoggel D, Vásquez-Jiménez W, Verhoef C, Vierimaa M, Vizzielli G, Voogt ELK, Uehara K, Wakeman C, Warrier S, Wasmuth HH, Weber K, Weiser MR, Westney OL, Wheeler JMD, Wild J, Wilson M, Wolthuis A, Yano H, Yip B, Yip J, Yoo RN, Zappa MA, Winter DC.

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All collaborators are members of The PelvEx Collaborative.

Competing interests:
None declared.

PPI:
Patients and patient advocacy organisations were involved in the design, conduct, reporting and dissemination plans of this research. Refer to the methods section for further details.

Patient consent for publication:
Not required.

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References:

1. Johnson YL, West MA, Gould LE, Drami I, Behrenbruch C, Burns EM, et al. Empty pelvis syndrome: a systematic review of reconstruction techniques and their associated complications. Colorectal Disease. 2022;24(1):16-26.
2. Barber HRKJ, J.C. Pelvic Exenteration. In: Nichols DH, editor. Gynecologic and Obstetric Surgery. St Louis, Missouri: Mosby - Year Book, Inc.; 1993. p. 682.
3. Martínez-Gómez C, Angeles MA, Martinez A, Malavaud B, Ferron G. Urinary diversion after pelvic exenteration for gynecologic malignancies. Int J Gynecol Cancer. 2021;31(1):1-10.
4. Robertson G, Lopes A, Beynon G, Monaghan JM. Pelvic exenteration: a review of the Gateshead experience 1974-1992. Br J Obstet Gynaecol. 1994;101(6):529-31.
5. Finan MA, Fiorica JV, Hoffman MS, Barton DP, Gleeson N, Roberts WS, et al. Massive pelvic hemorrhage during gynecologic cancer surgery: "pack and go back". Gynecol Oncol. 1996;62(3):390-5.
6. Ghosh PS, Fawzi H. Empty pelvis syndrome. J Obstet Gynaecol. 2004;24(6):714-5.
7. L P. Reconstruction of the pelvic floor and management of the empty pelvis; correction of pelvic hernias. Nogyogyaszati Onkologia. 1998;2:175-6.

8. Bacalbasa N, Tomescu D, Balescu I. Use of Inflated Foley Catheters to Prevent Early Empty Pelvis Complications Following Pelvic Exenteration. Anticancer Research. 2015;35(10):5543-6.
9. Ferron G, Gangloff D, Querleu D, Frigenza M, Torrent JJ, Picaud L, et al. Vaginal reconstruction with pedicled vertical deep inferior epigastric perforator flap (diep) after pelvic exenteration. A consecutive case series. Gynecol Oncol. 2015;138(3):603-8.
10. Cortinovis U, Sala L, Bonomi S, Gallino G, Belli F, Ditto A, et al. Rectus Abdominis Myofascial Flap for Vaginal Reconstruction After Pelvic Exenteration. Ann Plast Surg. 2018;81(5):576-83.
11. Lee P, Tan WJ, Brown KGM, Solomon MJ. Addressing the empty pelvic syndrome following total pelvic exenteration: does mesh reconstruction help? Colorectal Disease. 2019;21(3):365-9.
12. Carboni F, Federici O, Giofre M, Zazza S, Valle M. Empty pelvis syndrome: the use of breast prosthesis in the prevention of complications. Colorectal Dis. 2019;21(11):1321-5.
13. Lau YC, Brown KGM, Lee P. Pelvic exenteration for locally advanced and recurrent rectal cancer-how much more? J Gastrointest Oncol. 2019;10(6):1207-14.
14. Tuech JJ, Pinson J, Nouhaud FX, Wood G, Clavier T, Sabourin JC, et al. Total Pelvic Exenteration, Cytoreductive Surgery, and Hyperthermic Intraperitoneal Chemotherapy for Rectal Cancer with Associate Peritoneal Metastases: Surgical Strategies to Optimize Safety. Cancers (Basel). 2020;12(11).
15. Bankar S, Desouza A, Paliwal V, Pandey D, Gori J, Sukumar V, et al. Novel use of the Bakri balloon to minimize empty pelvis syndrome following laparoscopic total pelvic exenteration. Colorectal Dis. 2020;22(12):2322-5.
16. Manzour N, Vázquez-Vicente D, Carriles I, Boria F, Chacon E, Chiva L. Intra-operative radiation therapy after a total lateral extended infralevator exenteration for recurrent cervical cancer. Int J Gynecol Cancer. 2021;31(8):1188-9.
17. Ng KS, Lee PJM. Pelvic exenteration: Pre-, intra-, and post-operative considerations. Surg Oncol. 2021;37:101546.
18. Wang Y, Wang P. Novel technique with bladder peritoneum to prevent empty pelvic syndrome after laparoscopic pelvic exenteration for gynecologic malignancies: Three case reports. Medicine (Baltimore). 2021;100(49):e28200.
19. PelvEx Collaborative. Contemporary Management of Locally Advanced and Recurrent Rectal Cancer: Views from the PelvEx Collaborative. Cancers (Basel). 2022;14(5).
20. Omarov N, Uymaz DS, Bugra D. Different uses of the breast implant to prevent empty pelvic complications following pelvic exenteration. BMJ Case Rep. 2022;15(3).
21. Persson P, Chong P, Steele CW, Quinn M. Prevention and management of complications in pelvic exenteration. Eur J Surg Oncol. 2022;48(11):2277-83.
22. Wang J, Prabhakaran S, Larach T, Warrier SK, Bednarski BK, Ngan SY, et al. Treatment strategies for locally recurrent rectal cancer. Eur J Surg Oncol. 2022;48(11):2292-8.
23. Shine RJ, Glyn T, Frizelle F. Pelvic exenteration: a review of current issues/controversies. ANZ J Surg. 2022.
24. Kazi M, Desouza A, Bankar S, Jajoo B, Dohale S, Vadodaria D, et al. The use of an obstetric balloon as a pelvic spacer in preventing empty pelvis syndrome after total pelvic exenteration in rectal cancers - A prospective safety and efficacy study for the Bakri balloon. Colorectal Dis. 2022.

25. Sutton PA, Brown KGM, Ebrahimi N, Solomon MJ, Austin KKS, Lee PJ. Long term surgical complications following pelvic exenteration - operative management of the empty pelvis syndrome. Colorectal Dis. 2022.
26. Khaw CW, Ebrahimi N, Lee P, McCarthy ASE, Solomon M. Long-term results of mesh pelvic floor reconstruction to address the empty pelvis syndrome. Colorectal Dis. 2022.
27. Manzour N, Boria F, Chiva L. Empty pelvis syndrome: is there an easy way? Int J Gynecol Cancer. 2022;32(1):114.
28. Aminimoghaddam S, Hivehchi N, Ghaemi M, Eshghinejad A, Yazdizadeh M. Using Bakri balloon as a visceral replacement for occupying pelvic cavity in pelvic exenteration, a case report. Int J Surg Case Rep. 2022;99:107646.
29. de-la-Noval BD, Zapardiel I, Etemandi SZ, Gutierrez A, Garcia J, Tejeda MDD. A New Proposal of Pelvic Floor Reconstruciton Using Biosynthetic Mesh after Abdominoperineal Radical Surgery in Gynecological: A Case Series. International Journal of Gynecology & Clinical Practices. 2017;4:131.
30. Venchiarutti RL, Solomon MJ, Koh CE, Young JM, Steffens D. Pushing the boundaries of pelvic exenteration by maintaining survival at the cost of morbidity. Br J Surg. 2019;106(10):1393-403.
31. James Lind Alliance. Living With and Beyond Cancer 2018 [Available from: https://www.jla.nihr.ac.uk/priority-setting-partnerships/living-with-and-beyond-cancer/].
32. Jünger S, Payne SA, Brine J, Radbruch L, Brearley SG. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. Palliat Med. 2017;31(8):684-706.
33. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017;18(Suppl 3):280.
34. Gorst SL, Prinsen CAC, Salcher-Konrad M, Matvienko-Sikar K, Williamson PR, Terwee CB. Methods used in the selection of instruments for outcomes included in core outcome sets have improved since the publication of the COSMIN/COMET guideline. J Clin Epidemiol. 2020;125:64-75.
35. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. PLoS Med. 2016;13(10):e1002148.
36. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STAndardised Protocol Items: the COS-STAP Statement. Trials. 2019;20(1):116.
37. West CT, West MA, Mirnezami AH. Pathophysiology, mitigation, and a core outcome set for the empty pelvis syndrome after pelvic exenteration: a Delphi-study by the PelvEx Collaborative 2023 [Available from: https://www.comet-initiative.org/Studies/Details/2539].
38. Management strategies for patients with advanced rectal cancer and liver metastases using modified Delphi methodology: results from the PelvEx Collaborative. Colorectal Dis. 2020;22(9):1184-8.
39. Perioperative management and anaesthetic considerations in pelvic exenterations using Delphi methodology: results from the PelvEx Collaborative. BJS Open. 2021;5(1).
40. Powell C. The Delphi technique: myths and realities. J Adv Nurs. 2003;41(4):376-82.
41. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.
42. Blazeby JM, Macefield R, Blencowe NS, Jacobs M, McNair AG, Sprangers M, et al. Core information set for oesophageal cancer surgery. Br J Surg. 2015;102(8):936-43.

43. Innes K, Hudson J, Banister K, Croal B, Ramsay C, Ahmed I, et al. Core outcome set for symptomatic uncomplicated gallstone disease. Br J Surg. 2022.
44. Sousa-Uva M, Head SJ, Thielmann M, Cardillo G, Benedetto U, Czerny M, et al. Methodology manual for European Association for Cardio-Thoracic Surgery (EACTS) clinical guidelines. Eur J Cardiothorac Surg. 2015;48(6):809-16.
45. McNutt MK, Bradford M, Drazen JM, Hanson B, Howard B, Jamieson KH, et al. Transparency in authors' contributions and responsibilities to promote integrity in scientific publication. Proc Natl Acad Sci U S A. 2018;115(11):2557-60.

Core Outcome Set-STAndardised Protocol Items (COS-STAP) statement:

TITLE/ABSTRACT		
Title	1a	Identify in the title that the paper describes the protocol for the planned development of a COS *Title is – "Beating the Empty Pelvis Syndrome: The PelvEx Collaborative Core Outcome Set Study Protocol"*
Abstract	1b	Provide a structured abstract *Abstract provided.*
INTRODUCTION		
Background and objectives	2a	Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation *Provided rationale in introduction, and barriers in limitations section*
	2b	Describe the specific objectives with reference to developing a COS *Provided in aims and objectives section.*
Scope	3a	Describe the health condition(s) and population(s) that will be covered by the COS *Patients undergoing pelvic exenteration at risk of empty pelvis syndrome.*
	3b	Describe the intervention(s) that will be covered by the COS *Pelvic exenteration.*
	3c	Describe the context of use for which the COS is to be applied *Research into empty pelvis syndrome, specifically by the PelvEx Collaborative following completion of this study.*
METHODS		
Stakeholders	4	Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study *Formation of study steering committee, and both expert groups (healthcare professionals and patient representatives).*
Information	5a	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference

sources		other protocols/papers *Described the long listing process of statements, which is described in full in the protocol paper.*
	5b	Describe how outcomes may be dropped/combined, with reasons *Described how statements will be dropped or added depending on consensus scores and thematic analysis from open questions. Described how third Delphi round may be required to drop further core outcome set statements if too many items are retained after the second Delphi round.*
Consensus process	6	Describe the plans for how the consensus process will be undertaken *Described the modified-Delphi process, and how this leads into consensus meetings.*
Consensus definition	7a	Describe the consensus definition *Definition of consensus is defined a priori for the modified-Delphi process.*
	7b	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process *This is described using mixture of modified-Delphi, thematic analysis, and consensus meetings.*
ANALYSIS		
Outcome scoring/feedback	8	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process *This is described – using histograms, interquartile ranges, and medians displayed on Qualtrics survey software.*
Missing data	9	Describe how missing data will be handled during the consensus process *Forced response function will be used on Qualtrics to prevent missing data occurring.*
ETHICS and DISSEMINATION		
Ethics approval/informed consent	10	Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant) *Ethics is obtained from University of Southampton, informed consent process is described.*
Dissemination	11	Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination *This is described in the ethics and dissemination section.*
ADMINISTRATIVE INFORMATION		

Funders	12	Describe sources of funding, role of funders *Funders for the study have been listed.*
Conflicts of interest	13	Describe any potential conflicts of interest within the study team and how they will be managed *No competing interests exist.*

Guidance on Conducting and REporting DElphi Studies (CREDES): Note steps 8 to 16 on Delphi reporting standards are not applicable to the protocol paper.

Rationale for choice of the Delphi technique:

1. Justification – the choice of a Delphi as a method for systematically collating expert consultation and building consensus needs to be well justified.
   Empty pelvis syndrome requires consensus across the domains described to facilitate further progress in this field of research.

Planning and design:

2. Planning and process – the Delphi technique is a flexible method that can be adjusted to research aims and purposes, any modifications should be justified by rationale and be applied systematically and rigorously.
   Aims are defined clearly, the decision making for the protocol is detailed systematically throughout to demonstrate rationale.

3. Definition of consensus – the criterion for consensus should be define *a priori* including guidance on how to proceed if consensus is not reached, or is reached early.
   Decisions on consensus are defined a priori and published on the clinicaltrials.gov site – methods for reaching consensus early or not at all are stated.

Study conduct:

4. Informational input – all material provided to the expert panel at the outset otf the project and through the Delphi process should be carefully reviewed and piloted in advance of dissemination.
   Prior to the Delphi commencing a piloting round was completed, which is described here. Before commencing the Delphi process all study material was reviewed by the steering committee, which included a PPI professional to ensure patient facing material was appropriate.

5. Prevention of bias – researchers need to take measures to avoid directly or indirectly influencing experts' judgements.
   Statements will be ordered in alphabetical order when presented to avoid leading question bias, there were no conflicts of interest among the steering committee.

6. Interpretation and processing of results – consensus does not necessarily imply the 'correct answer' or judgement, it should be noted that non-consensus and stable disagreement provide informative insights.
   Statements and suggestions for statements will be included in the Delphi and subsequent Delphi rounds in a minimally non-selective way, including some contradictory statements. Statements that do no reach consensus will also be presented within the results.

7. External validation – it is recommended to have the final draft of the resulting guidance reviewed by an external authority before publication and dissemination.
   A contact on in a colorectal professional association has been made with the intention for that individual to facilitate external review.

Core Outcome Set-STAandards for Reporting (COS-STAR) Guidelines: These guidelines will be used when reporting the final study paper.

SECTION/TOPIC	ITEM No.	CHECKLIST ITEM
TITLE/ABSTRACT		
Title	1a	Identify in the title that the paper reports the development of a COS
Abstract	1b	Provide a structured summary
INTRODUCTION		
Background and Objectives	2a	Describe the background and explain the rationale for developing the COS.
	2b	Describe the specific objectives with reference to developing a COS.
Scope	3a	Describe the health condition(s) and population(s) covered by the COS.
	3b	Describe the intervention(s) covered by the COS.
	3c	Describe the setting(s) in which the COS is to be applied.
METHODS		
Protocol/Registry Entry	4	Indicate where the COS development protocol can be accessed, if available, and/or the study registration details.
Participants	5	Describe the rationale for stakeholder groups involved in the COS development process, eligibility criteria for participants from each group, and a description of how the individuals involved were identified.
Information Sources	6a	Describe the information sources used to identify an initial list of outcomes.
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable).
Consensus Process	7	Describe how the consensus process was undertaken.
Outcome Scoring	8	Describe how outcomes were scored and how scores were summarised.
Consensus Definition	9a	Describe the consensus definition.
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process.
Ethics and Consent	10	Provide a statement regarding the ethics and consent issues for the study.
RESULTS		
Protocol Deviations	11	Describe any changes from the protocol (if applicable), with reasons, and describe what impact these changes have on the results.
Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COS development.
Outcomes	13a	List all outcomes considered at the start of the consensus process.
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process.
COS	14	List the outcomes in the final COS.
DISCUSSION		
Limitations	15	Discuss any limitations in the COS development process.
Conclusions	16	Provide an interpretation of the final COS in the context of other evidence, and implications for future research.
OTHER INFORMATION		
Funding	17	Describe sources of funding/role of funders.
Conflicts of Interest	18	Describe any conflicts of interest within the study team and how these were managed.

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Beating the Empty Pelvis Syndrome: The PelvEx Collaborative Core Outcome Set Study Protocol

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Beating the Empty Pelvis Syndrome: The PelvEx Collaborative Core Outcome Set Study Protocol

Edited for BMJ Open

Author:

Collaborative, PelvEx

Abstract:

Introduction:

The empty pelvis syndrome is a significant source of morbidity following pelvic exenteration surgery. It remains poorly defined with research in this field being heterogenous and of low quality. Furthermore, there has been minimal engagement with patient representatives following pelvic exenteration with respect to the empty pelvic syndrome. "PelvEx – Beating the empty pelvis syndrome" aims to engage both patient representatives and healthcare professionals to achieve an international consensus on a core outcome set, pathophysiology, and mitigation of the empty pelvis syndrome.

Methods and analysis:

A modified-Delphi approach will be followed with a three-stage study design. Firstly, statements will be longlisted using a recent systematic review, healthcare professional event, patient and public engagement, and Delphi piloting. Secondly, statements will be shortlisted using up to three rounds of online modified-Delphi. Thirdly, statements will be confirmed and instruments for measurable statements selected using a virtual patient-representative consensus meeting, and finally a face-to-face healthcare professional consensus meeting.

Ethics and dissemination:

The University of Southampton Faculty of Medicine ethics committee has approved this protocol, which is registered as a study with the Core Outcome Measures in Effectiveness Trials Initiative. Publication of this study will increase the potential for comparative research to further understanding and prevention of the empty pelvis syndrome.

ClinicalTrials.gov registration number: NCT05683795

Strengths and limitations (up to 5 bullet points needed):

- The study intends to internationally recruit diverse groups of patient representatives and healthcare professionals.
- Patient representation has been sought from an early stage to ensure this project captures patient perspectives.
- The protocol proposes to generate core outcome and core descriptor sets that are measurable.
- Recruitment of international non-English patient representatives may be challenging as this study has been designed in the UK with chiefly UK-based patient advocacy groups.

Introduction:

Pelvic exenteration encompasses radical, multi-visceral surgery for locally advanced primary and locally recurrent pelvic malignancies. It is hypothesised that the empty space created following pelvic exenteration can result in a sequelae of complications such as infected pelvic collections, prolonged ileus, mechanical bowel obstruction, perineal sinus, and entero-perineal fistula. This pathological process has been termed, "the empty pelvis syndrome" (EPS). Morbidity relating to EPS is estimated to be responsible for up to 40% of complications following pelvic exenteration (1).

EPS was first defined in 1993 by Barber et al, as "*A flulike illness with malaise, elevated temperature, and increased discharge from the perineal sinus that may continue for many years, particularly among those undergoing heavy irradiation* (2). The same condition has also been labelled as 'the empty pelvic syndrome' or 'pelvic burn syndrome' (3). There is presently renewed interest in EPS, with five publications making reference to it between 1993 – 2014 (2, 4-7), and twenty-four papers between 2015 – 2022 (1, 3, 8-29). These citations give inconsistent definitions and outcomes for EPS. As a result, there is limited scope for meta-analyses that may help guide prevention and management of this syndrome. A recent systematic review on reconstructive techniques for EPS cited low quality evidence with small patient numbers, precluding the ability to provide evidence-based recommendations as to the most appropriate reconstructive technique (1).

The anatomical and pathophysiological mechanisms behind EPS are largely undefined. Major bone or nerve resections have been shown to result in surgical intervention for complications related to EPS. These factors may be surrogate markers for more extensive surgery (25). In recent years, more radical pelvic exenterations are being performed along with the addition of intra-operative oncological strategies like intra-operative radiotherapy, in an attempt to improve oncological outcomes for patients (19, 30). The degree of morbidity and the number of patients affected by EPS are therefore likely to increase. The formulation of a consensus definition for EPS, with a measurable core outcome and core descriptor set would limit heterogeneity of data reporting, enhancing the quality of the evidence base, with the aim of improving outcomes for patients undergoing pelvic exenteration.

Patients are key stakeholders in this process, however to date they have not had an active role in design and participation in any research on EPS. The UK National Cancer Research Institute and James Lind Alliance partnership have defined the Living With and Beyond Cancer Top 10 Priorities, and this study dovetails with several of these priorities (31):

- The consequences of EPS can be implicated in the persistent late effects of cancer treatments.
- Patients eligible for pelvic exenteration have complex needs with often several surgical and oncological teams involved in their care
- The psychological impact of EPS is under-reported with no data captured in this area.
- The pathophysiology of EPS currently is poorly understood; and addressing this will lead to improved treatments.
- A defined core outcome set and core descriptor set will enable better prediction of which patients are at risk of developing EPS post-surgery.

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched on 14/07/2022 and there were no references to pelvic exenteration, complex pelvic cancer, or EPS. A three-stage study design using healthcare professionals and patient representatives as stakeholders will be followed:

1. Longlisting statements through systematic review, healthcare professional event, patient and public engagement (PPI) and piloting
2. Shortlisting statements using up to three rounds of online modified-Delphi
3. Confirming statements with a patient-representative virtual consensus meeting, and a face-to-face healthcare professional consensus meeting

Aims and objectives:

The primary aim of this study is to define a measurable core outcome set for EPS involving both healthcare professionals and patient representatives as stakeholders.

Secondary aims include:

- Establishing consensus on the pathophysiology of EPS with a view to forming a written definition and a measurable core descriptor set.
- Exploration of consensus on the reconstructive techniques that can be used to mitigate the effects of EPS.

Methods and analysis:

This study has been designed in accordance with Guidance on Conducting and REporting DElphi Studies (CREDES), the COMET handbook, Consensus-based Standards for the selection of health Measurement Instruments (COSMIN)/COMET guidance, Core Outcome Set-STAndardised Protocol Items (COS-STAP) statement, and Core Outcome Set-STAandards for Reporting (COS-STAR) Guidelines (32-36). It has been registered on the COMET database (37) and ClinicalTrials.gov (NCT05683795).

Patient and public involvement:

Two separate expert groups were formed for this study, patient representatives and healthcare professionals. Patient and public involvement (PPI) using local networks was established during the design stage of the study with patient representatives joining the project steering committee. Further PPI engagement was established by involving the Bowel Research UK People and Research Together (BRUK PaRT) programme, CommunitiesFirst, and World Federation of Incontinence and Pelvic Problems. This ensured patient facing study materials were appropriate, and that patient representatives contributed directly to creating

the longlist of statements. Patients will be invited to participate in the study utilising these networks, with BRUK PaRT also advertising the study for patient representatives through social media.

Expert groups:

The PelvEx Collaborative is a diverse international group of healthcare professionals from 140 hospitals across five continents that provide pelvic exenteration services. The PelvEx Collaborative have previously undertaken Delphi studies, therefore this is an ideal, motivated and logistically convenient platform to undertake a Delphi study due to its expertise, access to patients as key stakeholders, and the opportunity to undertake a face-to-face consensus meeting at the PelvEx Collaborative annual scientific meeting. (38, 39).

In a Delphi study there is no agreement on how a group of experts should be selected, and there is no need for a statistically representative sample to be obtained (40). An inclusive convenience sampling strategy will be used for both healthcare professionals and patient representatives with no upper limits set on sample size, this will avoid bias from selecting participants. All members of the PelvEx Collaborative will be invited to be involved in the study, generating, multi-professional, multi-national representation. Members of the PelvEx Collaborative will also be encouraged to engage their individual institutional PPI networks to participate in the project.

Stage 1 – creating an EPS statements longlist:

Statements were divided into three domains:

1. An EPS core outcome set
2. Pathophysiology of EPS
3. Mitigation of EPS

A recent systematic review and subsequently published literature on EPS were searched for statements in keeping with these domains (1, 25, 26). The PelvEx Collaborative held an international face-to-face meeting in Amsterdam in 2022 where an empty pelvis initiative was presented, and further statements were generated based on formal and informal discussions at this meeting. The study steering committee was then formed from an international group

of nine healthcare professionals, three patient representatives that had undergone pelvic exenteration, and PPI professionals from BRUK PaRT – further statements were then generated from opinions of this committee.

The study is sponsored by the University of Southampton who provide institutional access to the Qualtrics Survey software package. A pilot of the first Delphi round was produced based on the statements generated above and trialled with the study steering committee. This included open questions to generate further statements. The time taken for individuals to complete the pilot study was also timed to allow an approximation of the burden of time required by participants to be included in invitation letters. Following piloting, the study steering committee met to confirm the longlist of 70 statements for the first Delphi round, the number of statements for each domain was as follows:

1. An EPS core outcome set – 19 statements
2. Pathophysiology of EPS – 17 statements
3. Mitigation of the EPS – 34 statements

It was decided that patient representatives would only be invited to participate in the core outcome set domain, as it was felt they would be unlikely to have the experience in the other domains to provide helpful input into forming consensus. Statements in the core outcome set domain will therefore be presented in lay terms with technical language following this in parentheses.

Stage 2 – creating an EPS statement shortlist:

Three Delphi rounds are likely to be required with two separate stakeholder groups taking part; patient representatives and healthcare professionals. Members of the PelvEx Collaborative are experts in providing pelvic exenteration with experience of EPS, the healthcare professional stakeholder group will be recruited by contacting this group. The inclusion criteria for patient representatives is any individual that has undergone pelvic exenteration, which is defined as surgery to remove multiple organs from the pelvis, including beyond total mesorectal excision plane operations. This will include patients with any cancer (i.e., primary or recurrent colorectal, gynaecological, urological and connective tissue malignancies). Patient representatives will be sought through BRUK PaRT, CommunitiesFirst,

World Federation of Incontinence and Pelvic Problems, and by encouraging members of the PelvEx Collaborative to approach their individual institutional PPI networks. Patient representatives that do not speak English are also eligible to participate with translation of patient facing materials to be provided by LanguageInsight, and healthcare professionals from the PelvEx Collaborative able to appropriately translate information. In order to be able to describe the diversity of the stakeholder groups demographic information will be sought in the first Delphi round.

Potential participants will be emailed invitation letters along with a link to the Qualtrics first Delphi round. Before voting on statements Qualtrics will present participants with an informed consent form that must be completed first. Qualtrics will utilise the 'Force Response' function, therefore participants must complete all of a Delphi round before being able to submit. This will eliminate missing data from the study.

The first Delphi round will include all longlisted statements generated from stage 1 arranged in alphabetic order to reduce leading questions or researcher bias. These will be scored by participants from 1 – 9 on a Likert scale, as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (41). With 1 – 3 representing 'not important', 4 – 6 representing 'important but not critical' and 7 – 9 representing 'critical for inclusion.' A score of '0' will also be included, which will mean 'unable to comment.' The final questions on each domain will be open in order to avoid early closure of ideas among participants, so that further insight not anticipated in stage 1 of the process is gathered with the intention to generate new statements for the second round of the Delphi.

There is no recognised formal way of defining consensus in Delphi studies, however it is specified here *a priori* that in order for statements to progress they must obtain stricter consensus between subsequent rounds. To progress from the first round to the second round statements must be rated 7 – 9 by 50% or more of participants, and by 1 – 3 by no more than 15% of participants in at least one stakeholder group. Beyond round 2 retained items must be rated between 7 – 9 by over 70% of respondents, and by 1 – 3 by less than 15% by at least one stakeholder group. This method reduces the chance of dropping statements that may be

rated more highly in subsequent rounds once participants have received feedback that may indeed reach consensus, in addition separating analysis for patient representatives and healthcare professionals reduces the chance of statements deemed very important for one group being excluded. From piloting there was concern that a large proportion of statements for the core outcome set were rated as essential, therefore it was decided *a priori* that if there are 10 or more core outcome set statements reaching consensus by the end of a second round then a third Delphi round will take place, with higher level consensus required, defined as 95% participants voting 7 – 9 that the statement should be included. This would avoid inclusion of too many statements that could place increased time constraints on the consensus meetings process, and potentially limit the overall focus of the final core outcome set. These consensus agreement approaches are based on previous surgical core outcome set studies (42, 43).

Responses to open questions from the first round will undergo thematic analysis and will be used to formulate new statements for addition to subsequent rounds. Any comments that apply to particular statements, that are not able to be formulated into new statements will be presented verbatim in subsequent rounds alongside relevant statements. Open questions will not be included from the second round.

It is anticipated that each round will be open for one month with personalised email reminders issued to participants at 2 weeks and 48 hours from the deadline to encourage responses. Any participants wishing to drop out will be asked to give a reason for doing so, to facilitate recognition of any systematic attrition bias. Only individuals that completed the previous round will be contacted to take part in a subsequent round; if attrition leads to participation dripping below 70% of a previous round, the Delphi study will be terminated as below this level, rigor cannot be guaranteed. The study would then proceed directly to stage 3.

Analysis for patient representatives and healthcare professionals between rounds will take place separately. It is anticipated that more healthcare professionals will participate, therefore analysis of these two groups together would potentially reduce the importance given to the patient voice. There will be presentation of this separate analysis for subsequent

rounds using medians and interquartile ranges, with how individuals voted in a previous round also disseminated. Histograms will also be included to facilitate understanding for patient representatives unfamiliar with descriptive statistics.

If progression of the Delphi rounds deviates from the presented protocol, decisions on whether to stop or continue to the Delphi will be taken by the Delphi steering committee.

Stage 3 – finalising EPS statements:

Any statements reaching consensus by the end of stage 2 that are measurable will have options for instruments prepared in accordance with COSMIN/COMET guidance (34). All potential instruments for measurement will be selected using the opinion of the study steering committee and reviews of the relevant literature, which will include instrument feasibility assessments. These options will then be presented at consensus meetings.

PelvEx 2023 is the international meeting of the PelvEx Collaborative and would be an ideal time to hold a face-to-face consensus meeting for participating healthcare professionals. It was felt this meeting would not be appropriate for patient representatives as it will involve significant travel, patients may be heavily influenced by the opinions of healthcare professionals, and may not feel as able to voice their opinions in front of a large audience.

To increase the number of involved patient representatives a virtual consensus meeting for patient representatives will be held prior to PelvEx 2023, which will be supported by BRUK PaRT. Participants will be sent results from the final round of the Delphi including their individual final votes. Any non-English speaking patient representatives will also be invited to participate with an appropriate multi-lingual healthcare professional from the PelvEx Collaborative joining the meeting to allow translation. At the start of the meeting demographic information will be requested to allow reporting of diversity. Any statements retained from the final Delphi round for the core outcome set will be included and participants will be asked to anonymously vote on whether the statement should stay in, be removed, or whether they are unsure. Where there is no consensus or participants are unsure, then further discussion will take place with an effort to capture dissenting views to determine the nature of a polarised response, also considering whether statements overlap

and can be combined. Further voting will take place, followed by further discussion; if there is persistent disagreement a final round of voting will take place using a majority rule.

For the core outcome set statements felt to be important, possible instruments to measure these statements will be presented for approval. It is anticipated that selection of instruments for patients will be difficult as the evidence on their methodology is likely to be challenging to understand, however it is hoped that with support from research facilitators that patients will be able to judge relevance, comprehensiveness and comprehensibility of the available instruments. This meeting will be recorded for analysis and potential presentation of patients speaking at PelvEx 2023 to help healthcare professionals understand patient experience.

Prior to PelvEx 2023 the results of the final Delphi rounds, statements for voting, and the patient virtual consensus meeting will be sent out to participants, including how individuals that participated voted in the final Delphi round. A list of delegates at PelvEx 2023 will be obtained along with demographic information, and whether or not they were involved in stage 2 of the project. Anonymous voting will be across all three domains and will follow the same pattern as the patient representative meeting.

Measurable statements that are included will have their pre-determined instruments presented for voting. If there is only one possible feasible instrument then participants will be permitted to vote either for this instrument, or that a recommendation is made for development of new instruments or that additional validation studies are required. It is difficult to predict how many statements will be voted upon and discussed. A further round of online voting or virtual consensus meetings following PelvEx 2023 may be required. This will be at the discretion of the study steering committee.

By the end of stage 3 the following should have been achieved for each domain:

1. A measurable core outcome set for EPS
2. Statements on pathophysiology of EPS generating a measurable core descriptor set and contributing to a written definition of EPS

3. To have established where there is consensus on current reconstructive techniques used to mitigate EPS, which will be graded by strength of recommendation and level of evidence (44).

It is unclear what the anatomical and pathophysiological causes of EPS are, how it can be prevented, and how its sequelae can be measured. EPS can be life-threatening and its consequences difficult to manage. This represents an ongoing, urgent, unmet clinical and research need in this growing patient population. Through the longlisting process this consensus study will be grounded in previous published work, expert opinion and PPI. The modified-Delphi will be as inclusive as feasible, giving the opportunity for diverse groups of international stakeholders to suggest further statements and vote with an *a priori* consensus definition that will identify the most important aspects of EPS. Finally, by undertaking consensus meetings there will be an opportunity to highlight and address nuances that cannot be easily approached using an online survey platform. Obtaining agreement on core outcome and core descriptor sets that are measurable will generate consensus that can be immediately utilised to reduce research heterogeneity in this field.

Ethics and dissemination:

Ethical approval for this protocol has been given from the University of Southampton under the ERGO II reference number 77306. Further ethical approval from other institutions may be sought to approach respective patient representatives as required.

Any deviations from this protocol will be described and justified. Once stage 3 of the project is completed the project will be reviewed by an external board prior to publication and dissemination. This will be paper by the PelvEx Collaborative as per previous work, with utilisation of CRedIT taxonomy to encourage collaborators to engage with the process (38, 39, 45). Publication will be in peer reviewed journals and dissemination through professional collaborators and associated networks to ensure international adoption. In addition, the patient advocacy groups involved will also assist in dissemination of the research.

Author affiliations:

All collaborators are members of The PelvEx Collaborative.

Funding:
The study coordinator, Mr Charles West, is a PhD candidate at University of Southampton and has received charitable funding from Bowel Research UK to run this study (BRUK SG23109). He is also sponsored by Penguins Against Cancer and PLANETS Cancer Charity.

Competing interests:
None declared.

PPI:
Patients and patient advocacy organisations were involved in the design, conduct, reporting and dissemination plans of this research. Refer to the methods section for further details.

Patient consent for publication:
Not required.

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Contributors:
PelvEx Collaborative members contributed to the design of this study protocol.

Collaborators:
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References:

1. Johnson YL, West MA, Gould LE, Drami I, Behrenbruch C, Burns EM, et al. Empty pelvis syndrome: a systematic review of reconstruction techniques and their associated complications. Colorectal Disease. 2022;24(1):16-26.
2. Barber HRKJ, J.C. Pelvic Exenteration. In: Nichols DH, editor. Gynecologic and Obstetric Surgery. St Louis, Missouri: Mosby - Year Book, Inc.; 1993. p. 682.
3. Martínez-Gómez C, Angeles MA, Martinez A, Malavaud B, Ferron G. Urinary diversion after pelvic exenteration for gynecologic malignancies. Int J Gynecol Cancer. 2021;31(1):1-10.
4. Robertson G, Lopes A, Beynon G, Monaghan JM. Pelvic exenteration: a review of the Gateshead experience 1974-1992. Br J Obstet Gynaecol. 1994;101(6):529-31.
5. Finan MA, Fiorica JV, Hoffman MS, Barton DP, Gleeson N, Roberts WS, et al. Massive pelvic hemorrhage during gynecologic cancer surgery: "pack and go back". Gynecol Oncol. 1996;62(3):390-5.
6. Ghosh PS, Fawzi H. Empty pelvis syndrome. J Obstet Gynaecol. 2004;24(6):714-5.
7. L P. Reconstruction of the pelvic floor and management of the empty pelvis; correction of pelvic hernias. Nogyogyaszati Onkologia. 1998;2:175-6.
8. Bacalbasa N, Tomescu D, Balescu I. Use of Inflated Foley Catheters to Prevent Early Empty Pelvis Complications Following Pelvic Exenteration. Anticancer Research. 2015;35(10):5543-6.
9. Ferron G, Gangloff D, Querleu D, Frigenza M, Torrent JJ, Picaud L, et al. Vaginal reconstruction with pedicled vertical deep inferior epigastric perforator flap (diep) after pelvic exenteration. A consecutive case series. Gynecol Oncol. 2015;138(3):603-8.
10. Cortinovis U, Sala L, Bonomi S, Gallino G, Belli F, Ditto A, et al. Rectus Abdominis Myofascial Flap for Vaginal Reconstruction After Pelvic Exenteration. Ann Plast Surg. 2018;81(5):576-83.
11. Lee P, Tan WJ, Brown KGM, Solomon MJ. Addressing the empty pelvic syndrome following total pelvic exenteration: does mesh reconstruction help? Colorectal Disease. 2019;21(3):365-9.
12. Carboni F, Federici O, Giofre M, Zazza S, Valle M. Empty pelvis syndrome: the use of breast prosthesis in the prevention of complications. Colorectal Dis. 2019;21(11):1321-5.
13. Lau YC, Brown KGM, Lee P. Pelvic exenteration for locally advanced and recurrent rectal cancer-how much more? J Gastrointest Oncol. 2019;10(6):1207-14.
14. Tuech JJ, Pinson J, Nouhaud FX, Wood G, Clavier T, Sabourin JC, et al. Total Pelvic Exenteration, Cytoreductive Surgery, and Hyperthermic Intraperitoneal Chemotherapy for Rectal Cancer with Associate Peritoneal Metastases: Surgical Strategies to Optimize Safety. Cancers (Basel). 2020;12(11).
15. Bankar S, Desouza A, Paliwal V, Pandey D, Gori J, Sukumar V, et al. Novel use of the Bakri balloon to minimize empty pelvis syndrome following laparoscopic total pelvic exenteration. Colorectal Dis. 2020;22(12):2322-5.
16. Manzour N, Vázquez-Vicente D, Carriles I, Boria F, Chacon E, Chiva L. Intra-operative radiation therapy after a total lateral extended infralevator exenteration for recurrent cervical cancer. Int J Gynecol Cancer. 2021;31(8):1188-9.
17. Ng KS, Lee PJM. Pelvic exenteration: Pre-, intra-, and post-operative considerations. Surg Oncol. 2021;37:101546.
18. Wang Y, Wang P. Novel technique with bladder peritoneum to prevent empty pelvic syndrome after laparoscopic pelvic exenteration for gynecologic malignancies: Three case reports. Medicine (Baltimore). 2021;100(49):e28200.

19. Contemporary Management of Locally Advanced and Recurrent Rectal Cancer: Views from the PelvEx Collaborative. Cancers (Basel). 2022;14(5).
20. Omarov N, Uymaz DS, Bugra D. Different uses of the breast implant to prevent empty pelvic complications following pelvic exenteration. BMJ Case Rep. 2022;15(3).
21. Persson P, Chong P, Steele CW, Quinn M. Prevention and management of complications in pelvic exenteration. Eur J Surg Oncol. 2022;48(11):2277-83.
22. Wang J, Prabhakaran S, Larach T, Warrier SK, Bednarski BK, Ngan SY, et al. Treatment strategies for locally recurrent rectal cancer. Eur J Surg Oncol. 2022;48(11):2292-8.
23. Shine RJ, Glyn T, Frizelle F. Pelvic exenteration: a review of current issues/controversies. ANZ J Surg. 2022.
24. Kazi M, Desouza A, Bankar S, Jajoo B, Dohale S, Vadodaria D, et al. The use of an obstetric balloon as a pelvic spacer in preventing empty pelvis syndrome after total pelvic exenteration in rectal cancers - A prospective safety and efficacy study for the Bakri balloon. Colorectal Dis. 2022.
25. Sutton PA, Brown KGM, Ebrahimi N, Solomon MJ, Austin KKS, Lee PJ. Long term surgical complications following pelvic exenteration - operative management of the empty pelvis syndrome. Colorectal Dis. 2022.
26. Khaw CW, Ebrahimi N, Lee P, McCarthy ASE, Solomon M. Long-term results of mesh pelvic floor reconstruction to address the empty pelvis syndrome. Colorectal Dis. 2022.
27. Manzour N, Boria F, Chiva L. Empty pelvis syndrome: is there an easy way? Int J Gynecol Cancer. 2022;32(1):114.
28. Aminimoghaddam S, Hivehchi N, Ghaemi M, Eshghinejad A, Yazdizadeh M. Using Bakri balloon as a visceral replacement for occupying pelvic cavity in pelvic exenteration, a case report. Int J Surg Case Rep. 2022;99:107646.
29. de-la-Noval BD, Zapardiel I, Etemandi SZ, Gutierrez A, Garcia J, Tejeda MDD. A New Proposal of Pelvic Floor Reconstruciton Using Biosynthetic Mesh after Abdominoperineal Radical Surgery in Gynecological: A Case Series. International Journal of Gynecology & Clinical Practices. 2017;4:131.
30. Venchiarutti RL, Solomon MJ, Koh CE, Young JM, Steffens D. Pushing the boundaries of pelvic exenteration by maintaining survival at the cost of morbidity. Br J Surg. 2019;106(10):1393-403.
31. James Lind Alliance. Living With and Beyond Cancer 2018 [Available from: https://www.jla.nihr.ac.uk/priority-setting-partnerships/living-with-and-beyond-cancer/].
32. Jünger S, Payne SA, Brine J, Radbruch L, Brearley SG. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. Palliat Med. 2017;31(8):684-706.
33. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017;18(Suppl 3):280.
34. Gorst SL, Prinsen CAC, Salcher-Konrad M, Matvienko-Sikar K, Williamson PR, Terwee CB. Methods used in the selection of instruments for outcomes included in core outcome sets have improved since the publication of the COSMIN/COMET guideline. J Clin Epidemiol. 2020;125:64-75.
35. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. PLoS Med. 2016;13(10):e1002148.
36. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STAndardised Protocol Items: the COS-STAP Statement. Trials. 2019;20(1):116.

37. West CT, West MA, Mirnezami AH. Pathophysiology, mitigation, and a core outcome set for the empty pelvis syndrome after pelvic exenteration: a Delphi-study by the PelvEx Collaborative 2023 [Available from: https://www.comet-initiative.org/Studies/Details/2539].
38. Management strategies for patients with advanced rectal cancer and liver metastases using modified Delphi methodology: results from the PelvEx Collaborative. Colorectal Dis. 2020;22(9):1184-8.
39. Perioperative management and anaesthetic considerations in pelvic exenterations using Delphi methodology: results from the PelvEx Collaborative. BJS Open. 2021;5(1).
40. Powell C. The Delphi technique: myths and realities. J Adv Nurs. 2003;41(4):376-82.
41. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.
42. Blazeby JM, Macefield R, Blencowe NS, Jacobs M, McNair AG, Sprangers M, et al. Core information set for oesophageal cancer surgery. Br J Surg. 2015;102(8):936-43.
43. Innes K, Hudson J, Banister K, Croal B, Ramsay C, Ahmed I, et al. Core outcome set for symptomatic uncomplicated gallstone disease. Br J Surg. 2022.
44. Sousa-Uva M, Head SJ, Thielmann M, Cardillo G, Benedetto U, Czerny M, et al. Methodology manual for European Association for Cardio-Thoracic Surgery (EACTS) clinical guidelines. Eur J Cardiothorac Surg. 2015;48(6):809-16.
45. McNutt MK, Bradford M, Drazen JM, Hanson B, Howard B, Jamieson KH, et al. Transparency in authors' contributions and responsibilities to promote integrity in scientific publication. Proc Natl Acad Sci U S A. 2018;115(11):2557-60.

Core Outcome Set-STAndardised Protocol Items (COS-STAP) statement:

TITLE/ABSTRACT		
Title	1a	Identify in the title that the paper describes the protocol for the planned development of a COS *Title is – "Beating the Empty Pelvis Syndrome: The PelvEx Collaborative Core Outcome Set Study Protocol"*
Abstract	1b	Provide a structured abstract *Abstract provided.*
INTRODUCTION		
Background and objectives	2a	Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation *Provided rationale in introduction, and barriers in limitations section*
	2b	Describe the specific objectives with reference to developing a COS *Provided in aims and objectives section.*
Scope	3a	Describe the health condition(s) and population(s) that will be covered by the COS *Patients undergoing pelvic exenteration at risk of empty pelvis syndrome.*
	3b	Describe the intervention(s) that will be covered by the COS *Pelvic exenteration.*
	3c	Describe the context of use for which the COS is to be applied *Research into empty pelvis syndrome, specifically by the PelvEx Collaborative following completion of this study.*
METHODS		
Stakeholders	4	Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study *Formation of study steering committee, and both expert groups (healthcare professionals and patient representatives).*
Information	5a	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference

sources		other protocols/papers *Described the long listing process of statements, which is described in full in the protocol paper.*
	5b	Describe how outcomes may be dropped/combined, with reasons *Described how statements will be dropped or added depending on consensus scores and thematic analysis from open questions. Described how third Delphi round may be required to drop further core outcome set statements if too many items are retained after the second Delphi round.*
Consensus process	6	Describe the plans for how the consensus process will be undertaken *Described the modified-Delphi process, and how this leads into consensus meetings.*
Consensus definition	7a	Describe the consensus definition *Definition of consensus is defined a priori for the modified-Delphi process.*
	7b	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process *This is described using mixture of modified-Delphi, thematic analysis, and consensus meetings.*
ANALYSIS		
Outcome scoring/feedback	8	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process *This is described – using histograms, interquartile ranges, and medians displayed on Qualtrics survey software.*
Missing data	9	Describe how missing data will be handled during the consensus process *Forced response function will be used on Qualtrics to prevent missing data occurring.*
ETHICS and DISSEMINATION		
Ethics approval/informed consent	10	Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant) *Ethics is obtained from University of Southampton, informed consent process is described.*
Dissemination	11	Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination *This is described in the ethics and dissemination section.*
ADMINISTRATIVE INFORMATION		

Funders	12	Describe sources of funding, role of funders *Funders for the study have been listed.*
Conflicts of interest	13	Describe any potential conflicts of interest within the study team and how they will be managed *No competing interests exist.*

Guidance on Conducting and REporting DElphi Studies (CREDES): Note steps 8 to 16 on Delphi reporting standards are not applicable to the protocol paper.

Rationale for choice of the Delphi technique:

1. Justification – the choice of a Delphi as a method for systematically collating expert consultation and building consensus needs to be well justified.
   Empty pelvis syndrome requires consensus across the domains described to facilitate further progress in this field of research.

Planning and design:

2. Planning and process – the Delphi technique is a flexible method that can be adjusted to research aims and purposes, any modifications should be justified by rationale and be applied systematically and rigorously.
   Aims are defined clearly, the decision making for the protocol is detailed systematically throughout to demonstrate rationale.

3. Definition of consensus – the criterion for consensus should be define *a priori* including guidance on how to proceed if consensus is not reached, or is reached early.
   Decisions on consensus are defined a priori and published on the clinicaltrials.gov site – methods for reaching consensus early or not at all are stated.

Study conduct:

4. Informational input – all material provided to the expert panel at the outset otf the project and through the Delphi process should be carefully reviewed and piloted in advance of dissemination.
   Prior to the Delphi commencing a piloting round was completed, which is described here. Before commencing the Delphi process all study material was reviewed by the steering committee, which included a PPI professional to ensure patient facing material was appropriate.

5. Prevention of bias – researchers need to take measures to avoid directly or indirectly influencing experts' judgements.
   Statements will be ordered in alphabetical order when presented to avoid leading question bias, there were no conflicts of interest among the steering committee.

6. Interpretation and processing of results – consensus does not necessarily imply the 'correct answer' or judgement, it should be noted that non-consensus and stable disagreement provide informative insights.
   Statements and suggestions for statements will be included in the Delphi and subsequent Delphi rounds in a minimally non-selective way, including some contradictory statements. Statements that do no reach consensus will also be presented within the results.

7. External validation – it is recommended to have the final draft of the resulting guidance reviewed by an external authority before publication and dissemination.
   A contact on in a colorectal professional association has been made with the intention for that individual to facilitate external review.

Core Outcome Set-STAandards for Reporting (COS-STAR) Guidelines: These guidelines will be used when reporting the final study paper.

SECTION/TOPIC	ITEM No.	CHECKLIST ITEM
TITLE/ABSTRACT		
Title	1a	Identify in the title that the paper reports the development of a COS
Abstract	1b	Provide a structured summary
INTRODUCTION		
Background and Objectives	2a	Describe the background and explain the rationale for developing the COS.
	2b	Describe the specific objectives with reference to developing a COS.
Scope	3a	Describe the health condition(s) and population(s) covered by the COS.
	3b	Describe the intervention(s) covered by the COS.
	3c	Describe the setting(s) in which the COS is to be applied.
METHODS		
Protocol/Registry Entry	4	Indicate where the COS development protocol can be accessed, if available, and/or the study registration details.
Participants	5	Describe the rationale for stakeholder groups involved in the COS development process, eligibility criteria for participants from each group, and a description of how the individuals involved were identified.
Information Sources	6a	Describe the information sources used to identify an initial list of outcomes.
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable).
Consensus Process	7	Describe how the consensus process was undertaken.
Outcome Scoring	8	Describe how outcomes were scored and how scores were summarised.
Consensus Definition	9a	Describe the consensus definition.
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process.
Ethics and Consent	10	Provide a statement regarding the ethics and consent issues for the study.
RESULTS		
Protocol Deviations	11	Describe any changes from the protocol (if applicable), with reasons, and describe what impact these changes have on the results.
Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COS development.
Outcomes	13a	List all outcomes considered at the start of the consensus process.
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process.
COS	14	List the outcomes in the final COS.
DISCUSSION		
Limitations	15	Discuss any limitations in the COS development process.
Conclusions	16	Provide an interpretation of the final COS in the context of other evidence, and implications for future research.
OTHER INFORMATION		
Funding	17	Describe sources of funding/role of funders.
Conflicts of Interest	18	Describe any conflicts of interest within the study team and how these were managed.

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