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Development of a Core Outcome Set to use in the Research and Assessment of Malignant Bowel Obstruction: protocol for the RAMBO study

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TITLE: Development of a Core Outcome Set to use in the Research and Assessment of Malignant Bowel Obstruction: protocol for the RAMBO study

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ABSTRACT

Introduction: Studies regarding the management of malignant bowel obstruction (MBO) report conflicting findings. This is partly due to different outcome measures being used to evaluate severity of MBO and the response to treatments. Furthermore, current outcome measures focus mainly on measurable physiological parameters which may not correlate strongly with patient-defined quality of life. The development of Core Outcome Sets allows a consistent approach to evaluating clinical conditions taking into consideration patient, health care professional and researcher viewpoints. It follows an internationally recognised standard methodology. We present a protocol for the development of a Core Outcome Set for Research and Assessment of Malignant Bowel Obstruction (RAMBO).

Methods: RAMBO is a multi-centre study, comprising of 4 phases: A systematic review to examine current scope of outcome measures associated with MBO (Phase 1). Interviews with patients, companions and health care professionals will explore priorities and preferences for care and outcomes (Phase 2). An expert panel meeting will collate the findings into a set of outcomes (Phase 3), refined by consensus through a Delphi survey with key stakeholders (Phase 4). The final set of outcomes will be ratified at a consensus meeting. Each step will actively include patient partners. Thematic analysis and descriptive statistics will be used to analyse qualitative and quantitative data respectively.

Ethics and dissemination: Ethical approval was obtained (Wales REC 5, REF: 19/LO/1876). Study participants and relevant stakeholders will be updated with newsletters and a lay summary at the end of the study. Abstracts will be submitted to national and international conferences, results papers will be submitted to peer reviewed, open access journals.

Study registration number: Core Outcome Measures in Effectiveness Trials (COMET) registration: 1402. Systematic Literature Review PROSPERO registration ID: CRD42019150648. Rapid Review PROSPERO registration ID: CRD42020176393

Strengths and limitations of the study

- The development of a Core Outcome Set for MBO will facilitate consistency of measurement across future clinical trials, allow effective evidence synthesis, and international involvement will enable broad dissemination and impact on clinical practice
- Recruitment will take place across different clinical settings and geographical areas, with populations in diverse socioeconomic areas. However, given the nature and prevalence of MBO, the patient sample for the interview study may be smaller than anticipated.
- Patients and their companions' views will be directly conveyed within the agreed measures, ensuring the outcomes are the ones important to patients and their companions.
- Patient partner involvement has occurred from the inception of the study and adheres to the UK PPI standards.
- Further work will be required to develop a single measurement instrument based on the Core Outcome Set.

Introduction

Malignant bowel obstruction (MBO) is bowel obstruction due to cancer or its treatments. It primarily affects people with advanced ovarian (10%-50%) and gastrointestinal cancers (15%) and remains a challenging condition facing oncology, surgical, gynaecology, gastroenterology and palliative care teams[1,2]. It is one of the most distressing complications of cancer, causing nausea, vomiting, abdominal distension, colic, pain and constipation[3-8]. It also has a persistent and profound effect on quality of life[9], and often requires hospitalisation for persistent unresolved symptoms[3].

Management options for MBO in patients with advanced cancer are limited; some, usually those with a single level bowel obstruction, may be offered surgery to resect an isolated tumour or create a de-functioning stoma. Some people may benefit from the endoscopic placement of a stent for palliative purposes. However, the majority of cases present with multiple level obstructions which are not amenable to surgical or endoscopic interventions. Pharmacological approaches for symptom reduction in inoperable MBO (IMBO) usually involve a combination of antiemetics and parenteral anti-secretory agents (anticholinergics, somatostatin analogues and H₂ antagonists), often with gut decompression (nasogastric tube or venting gastrostomy)[10-11].

Current evidence informing the symptom management of IMBO is inadequate; clinical guidelines favour somatostatin analogues but recommendations have been based, largely, on case series and insufficiently powered clinical trials[9]. Recently, two adequately powered, well-conducted clinical trials demonstrated no objective benefit with one of them suggesting evidence of harm[4, 12]. Importantly, these two trials included a placebo arm to reflect the natural history of IMBO, which is largely unknown, except that spontaneous resolution with recurrence is common and, for many people, it appears that vomiting will generally lessen in frequency and volume with time. However, these trials do not appear to have impacted on subsequent guidelines or clinical recommendations[13-16]; although there are some data showing they have affected clinical practice[17].

A recent systematic review of somatostatin analogues, using objective tools to evaluate data quality, concluded that there was moderate evidence of no benefit, and only poor evidence for their use[18]. The authors suggested that the most significant challenge in evaluating current data lay with the many studies using differing clinical outcomes, thereby making it impossible to objectively compare study outcomes or submit them to meta-analysis. The lack of an agreed core outcome set (COS) for MBO has considerable challenges in ensuring consistent clinical and research evaluation of interventions for patients with MBO.

Identifying outcome measures that reflect real-world settings

In order to ensure outcomes measures are relevant to patients, it is essential to have patients at the frontline of the research in order to ascertain their quality of life and preferences for symptom management and care. Patient reported outcomes (PROs), when collected and analysed appropriately, are key to shared decision making, clinical guidelines and health policy[19]. Involving patients' views and understanding the challenges they face are invaluable in understanding how care happens in real world settings, otherwise trials might fail to account for the outcomes that matter most to patients[20].

Rationale of COS development for MBO

A key issue identified on both a national and international level is the lack of data indicating how primary outcome measures used to evaluate MBO relate to patient experience[1, 17]. For example, measures of symptom relief may not directly reflect what is important to patients and their companions (next of kin/carers), and what they consider to be meaningful[18].

The broad and varied approaches to outcome measurement in the palliation of MBO, and the lack of an evidence base for patient-relevant measures, has led to a diversity of approach in clinical trials and inconsistent recommendations in clinical guidelines. Importantly, the continuation of poorly evidenced clinical practice may also cause harm[21]. Recent publications have called for the development of a COS, to ensure uniformity of symptom assessment within clinical trials and clinical practice[21]. This study aims to address this gap. It will ascertain patients' perceptions of the management of their condition, compare these with outcomes measured in the current literature, and gain consensus on an agreed set of core outcomes to be used in clinical practice to streamline appropriate and targeted management of MBO.

Aims

The RAMBO study aims to review the current scope of outcome measures used to evaluate MBO and to develop a set of core outcomes specific to MBO. It will ask the following questions:

1. What outcome measures are currently used to evaluate MBO within the context of clinical research and clinical practice?

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2. What symptoms and effects do patients with MBO, their companions and health care professionals consider most important, and what improvement would they consider clinically meaningful?
3. How do currently used outcomes map to those factors identified as important by patients, their companions and health care professionals, and what are the gaps and limitations in current measures?

Methods

Study design

We propose to use a multi-phase, mixed-method, multi-centre study to address the research questions. In Phase I, a systematic literature review will be conducted to identify outcomes currently used to evaluate MBO. Phase II will comprise of interviews with patients, their companions and health care professionals to understand their experiences, priorities and preferences for care. The findings of these two phases will inform Phase III, an expert panel meeting, to direct the compilation of a comprehensive list of outcomes which will feed into the Phase IV Delphi survey, a two-round ranking exercise followed by a consensus meeting. The aim of the Delphi is to achieve consensus on a final COS. A summary of the design can be seen in Figure 1. Dissemination will follow the Core Outcome Set-STAndards for Reporting (COS-STAR) Statement[22].

PPI – Patient and Public Involvement

We actively support the fundamental involvement of patient and public involvement (PPI) as set out by the UK Standards for Public Involvement in research in all of our research[23]. The RAMBO study has recruited two research partners (one of which is a co-applicant on the study) to represent lay stakeholders in the study management group advising on recruitment and participant-facing documentation. They will also contribute to thematic analysis of the interview data. Lay representatives will also be involved in the interpretation and dissemination of study results.

Phase I: Systematic Literature Review

The COMET Initiative recommends a systematic literature review (SLR) as an initial phase in studies developing COS[22]. This will identify all outcomes used in clinical trials and observational studies in patients undergoing palliative treatment for inoperable MBO. Qualitative papers will not be included as they do not quantify outcomes, but a separate, rapid review of qualitative studies will inform the writing up of the Phase II interview study (see below). Databases to be searched include MEDLINE, EMBASE, CINAHL, CareSearch and the Cochrane Central Register of Controlled Trials (CENTRAL). Other sources will include reference lists of included articles and of previous systematic reviews of MBO interventions, conference proceedings, grey literature, and the authors' own files. No date or language restrictions will be imposed.

The research questions that the review seeks to answer are:

- What outcome measures are used to evaluate clinical, symptomatic and psychological aspects of malignant bowel obstruction (MBO) within the context of clinical research and practice?
- How is the timing of outcome measures justified?
- Which outcome measures should be considered for inclusion in a COS for future clinical trials?

A broad range of study designs and heterogeneous data are anticipated in papers meeting the inclusion criteria for this review, and data will be explored using narrative synthesis. The review will record all clinical, symptomatic and psychological outcomes reported in included studies, with the definitions and time points of each measure, and review their heterogeneity and their relevance to patients with MBO. Data will be extracted and grouped with reference to the outcomes taxonomy recommended by COMET. The full protocol for the review, including the search strategy and study selection criteria, is available on the PROSPERO database, ID: [CRD42019150648](https://doi.org/10.1111/CRD4.2019150648).

Phase II: Interviews with patients, their companions and health care professionals

Participant eligibility and sampling

Interviews will explore the experiences of approximately 15 patients with MBO, what outcomes they would most value from their care, and the experiences of their companion if possible. In this case, companion if defined as a significant informal carer or family member (aged over 18). Patients eligible for interview will be adults aged 18 or over with histologically confirmed cancer, with their MBO currently or recently resolved but with risk of recurrence, as confirmed by either two senior medical practitioners or one medical practitioner in combination with confirmatory radiology. Patients will be interviewed with their carer/companion present if this is the patient's preference; carers/companions will be interviewed separately where this is preferred. We will not include patients who have any diagnosed medical problems that would prohibit them from participating in a 30-minute to 1-hour interview.

We will also interview approximately 15 healthcare professionals from a breadth of clinical specialities involved in the care of patients with MBO at the recruitment sites in the 12 months previous to recruitment, to explore the experiences involved in the management of MBO. Healthcare professionals will be purposively sampled to ensure a breadth of clinical specialties involved in the management of MBO, including primary care, palliative care, oncology, colorectal and gynaecological surgery.

The sample size of participants is based on past experience of patients receiving palliative care services across multiple studies and aims to reach data saturation – the point at which no new topics emerge. This will be achieved by constant re-evaluation and discussion between the two interviewers and with input from the study management team.

Data collection

A semi-structured interview format will be used to explore patients' understanding, experiences and symptoms of MBO, what matters most to patients with MBO, and what they consider to be a meaningful improvement regarding the relief of MBO symptoms. Interviews conducted with healthcare professionals will explore their experiences of managing MBO, how they evaluate severity and symptomatic response to treatment, what they perceive matters most to patients in regards to treatment of MBO, and how they perceive 'meaningful improvement' in a patient with MBO.

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3 Interviews are expected to last between 30 minutes and 1 hour. They will be undertaken in a quiet
4 location at participating hospitals or hospices or an alternative location of the participants' choice, at
5 a time specified by the participant.
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9 Interviews will be audio recorded on an encrypted recording device (with the participants' consent)
10 and uploaded onto a secure server, labelled with an identifying code, with no reference to personal
11 details. Audio files will be transcribed verbatim by an authorised agency. Basic demographic data will
12 be collected and reported descriptively but not used as sampling criteria. Transcripts will be checked
13 to ensure anonymisation by a member of the research team before being uploaded to NVivo12[24]
14 qualitative software for data management.
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22 Consent

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27 Written consent will be obtained at the outset of each interview. Individuals that lack the capacity to
28 consent will not be included in this study. Participant information sheets will be distributed to
29 potential participants by their clinical team, to give participants the time to make an informed decision
30 whether or not they wish to participate. If they choose to participate, they will inform a member of
31 their clinical team, who will pass on the patients' contact details to the researcher or the patient can
32 contact the researcher directly. The researcher will take written consent before the interview
33 commences; participants will have the chance to ask questions before the interview, and it will be
34 stressed to the participant that they are under no obligation to take part and may withdraw from the
35 study at any point during the interview, and that their participation has no influence on their medical
36 care.
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44 Healthcare professionals will be invited by email to participate in the study, with a follow-up email
45 after one week; eligible participants will be identified by the Clinical team, and the email will provide
46 them with a participant information sheet. If a potential participant expresses interest, they will be
47 asked to contact the researcher directly, or asked permission for the researcher to contact them. An
48 interview slot will be arranged at an appropriate time for the individual and written consent will be
49 taken by the researcher.
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Data Analysis

Thematic analysis[25] will be used to interrogate the interview data. Analysis will be conducted by two researchers, with experience in qualitative research, but no fixed views regarding the management or assessment of MBO. After an initial period of independent coding, meetings will be held between the two researchers to refine the themes and their concomitant categories. The analysis framework will be iteratively refined until all transcripts have been coded and a final thematic framework produced[25].

Findings from Phase I (systematic literature review) and Phase II (interviews) will be summarised in a report which addresses the main research question: What issues do patients, their companions and health care professionals consider to be most important in the management of symptoms of MBO, and what improvements would they consider meaningful? These data will also be synthesized with the qualitative data (Phase II interviews) identified through a rapid review of the qualitative literature. The report will seek to identify significant experiences and priorities among patients, their carers (if present) and health care professionals, that align with measurable outcomes[23] and can be taken forward into the initial outcomes list presented in Phase III.

Phase III: Steering Meeting and Expert Panel

A steering meeting will be held to consolidate the findings of the SLR and interview study, to produce a list of outcomes to be taken forward into Round 1 of the Delphi. The outcome list will be discussed and refined by an Expert Panel (consisting of approximately 10 academics/patient or carer research partners/healthcare professionals chosen for their recognised expertise in and/or experience of MBO), following CREDES guidelines for the Delphi technique[26].

Phase IV: Delphi Survey

The Delphi survey will be carried out using Online Survey UK, an electronic bespoke survey format which has previously been developed by the COMET Initiative for the use in COS development projects. A piloting round will be conducted with expert and lay members of the steering panel prior to wider stakeholder involvement. If issues needing resolution arise from this process, a second pilot

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3 round will be included. The survey will present the list of outcomes to stakeholders in two rounds,
4 with a final Consensus Meeting to resolve points of difference. The aim of the process is to reach
5 consensus, taking in a range of viewpoints: stakeholders will include patient representatives and
6 health care professionals in the area of clinical oncology, colorectal surgery, gastroenterology,
7 gynaecological surgery and specialist nursing. Anonymous results from the first round will be
8 circulated between all stakeholder groups as a basis for the subsequent round of decision-making.
9 Items on which the agreed threshold of consensus is reached in round one will be dropped from round
10 two. This technique is recognised by the COMET Initiative as appropriate to the development of
11 COS[23, 27].
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22 Recruitment

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26 Identification of potential patient research partners will take place in tandem with recruitment for
27 Phase II of the study, via the same recruitment channels, and through formal carer or bereavement
28 groups run by voluntary organisations. Healthcare professionals will be recruited from hospitals and
29 hospices, and by using the authors' professional networks. Participants will be recruited through
30 telephone, email or post. No new participants will be invited following the completion of Round 1.
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35 Based on recruitment numbers in previous studies and a pragmatic approach to reaching
36 consensus[28-29], we will aim to recruit a minimum of 40 respondents to take part, including
37 patients/companions, health care professionals and policy. Consent will be implicit through the
38 participants' registration to take part and completion of the survey. Each participant will be
39 represented in the survey documents by a unique identifier label; personal details will be kept
40 confidential in a separate database on secure on-line storage.
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49 Delphi Process

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53 The outcome list produced during Phase III will be used to construct the Delphi survey. Panel members
54 will be asked to score each outcome on a Likert scale ranging from 1 to 9[27] (1-3 – limited importance,
55 4-6 – important, 7-9 – critically important), relative to the other outcomes, in terms of the following
56 question:
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- Please consider each listed outcome, and rate how important it is to measure a change in the outcome when providing palliative care to address the symptoms of malignant bowel obstruction?

In addition to scoring outcomes, free text boxes will allow comments to be gathered on each item in each round of the survey, to make decision-making visible and assist other participants to refine their decision-making in the following round. This will allow respondents to add additional outcomes in order to address any perceived gaps in the way that patients' experiences are measured.

We anticipate two rounds to refine and rank outcomes in order to reach consensus, followed by a Consensus Meeting to resolve any items on which agreement is not reached. For each outcome in each round, the distribution of scores will be summarised, and items scored as of limited importance by all respondents will be dropped from subsequent rounds; all other items will be carried forward. The pre-set agreement criterion for scoring outcomes at each stage will be $\geq 70\%$, based on previous studies describing the development of COS[30-31]. Consensus will be reached if the majority of participants score a specific outcome similarly. Three categories will be assigned for each outcome:

- **Consensus: in** – 70% or more respondents within a stakeholder group rate the outcome as critically important, and 15% or fewer rate the outcome as of limited importance.
- **Consensus: out** – 70% or more of participants rated an outcome as of limited importance, and 15% or fewer rated the outcome as critically important.
- **No consensus** – none of the above criteria are met.

If 70 per cent or more of the respondents agree that an outcome is of low importance in Round 1, this item will be dropped from Round 2. If 70 per cent or more of respondents agree that an outcome is of high importance in Round 1, this item will be dropped from Round 2, and will be proposed for inclusion in the final core outcome set. All other items will be carried forward. In Round 2, participants will be shown the number of respondents and distribution of scores for each remaining outcome from all stakeholder groups, with their own score from Round 1. They will be asked to consider the responses from other Delphi participants, and to re-score the items. If a participant changes their score from of limited importance (<4 in Round 1) to critically important in Round 2 (7 or more) or from critically important in Round 1 to of limited importance in Round 2, they will be asked to provide the reason for this change. We will also examine any other changes in scores between rounds and summarise reasons given for these changes.

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3 Items on which agreement was not reached will be discussed and resolved at the final Consensus
4 Meeting. Outcomes from the Delphi survey classed as 'consensus in' across all groups will be proposed
5 for inclusion in the final COS; outcomes classed as 'consensus out' will be proposed for exclusion.
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10 11 Consensus Meeting

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16 All Delphi participants will be eligible for inclusion in a face-to-face Consensus Meeting to achieve a
17 final recommendation of a core set of outcomes. The survey registration page for Round 1 will ask
18 participants to tick a box to allow the study team to approach them for inclusion. Appropriate
19 secondary stakeholder groups recommended by existing stakeholders will be invited to take part at
20 this stage. Written consent will be taken at the outset of the meeting from all participants to audio
21 record the discussion; the audio file will be transcribed and anonymised. Participants will discuss all
22 outcomes and their status at the close of the survey. They will then vote on an outcome-by-outcome
23 basis to confirm consensus, or to suggest that an outcome requires further discussion. Further voting
24 rounds will be conducted as necessary until the final outcome set is agreed.
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35 Ethical Considerations

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38 Ethical approval for the study was obtained 10th December 2019, from Wales Research Ethics
39 Committee 5 Bangor (REF: 19/LO/1876). All data will be collected according to the principles of the
40 General Data Protection Regulations and Data Protection Act 2018[32].
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45 Dissemination

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47 The study is registered with the COMET database and dissemination through this will complement
48 peer review publications. Study participants and relevant bodies (e.g. health care professionals
49 involved in the management of MBO – including palliative care, gynaecology and colorectal surgery
50 and patient partner organisations) will be regularly updated with newsletters and a lay summary at
51 the end of the study. We will disseminate the research findings widely. Abstracts will be submitted to
52 national and international conferences, results papers will be to relevant stakeholders at international
53 conferences and submitted to publish in high impact, open access journals. Dissemination will be
54 undertaken with professional organisations such as the Association of Palliative Medicine (APM),
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3 European Association for Palliative Care (EAPC), The Multinational Association of Supportive Care in
4 Cancer (MASCC), The American Society of Clinical Oncology (ASCO), The European Society for Medical
5 Oncology (ESMO), National Cancer Research Institute (NCRI) and Hospice UK to adopt the
6 recommendations from the work. Lay summaries will be uploaded on the Marie Curie website,
7 including on the MCPCRC specific website and Wolfson Palliative Care Research Centre (WPCRC)
8 websites, and sent to key PPI groups and disseminated via social media.
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30 **Contribution:** All authors are on the trial steering committee (TSC) and have contributed equally to
31 the development of this study and the writing of the study protocol. EB and AB wrote the first draft of
32 this manuscript (and are joint first authors), with comments and contributions from all members of
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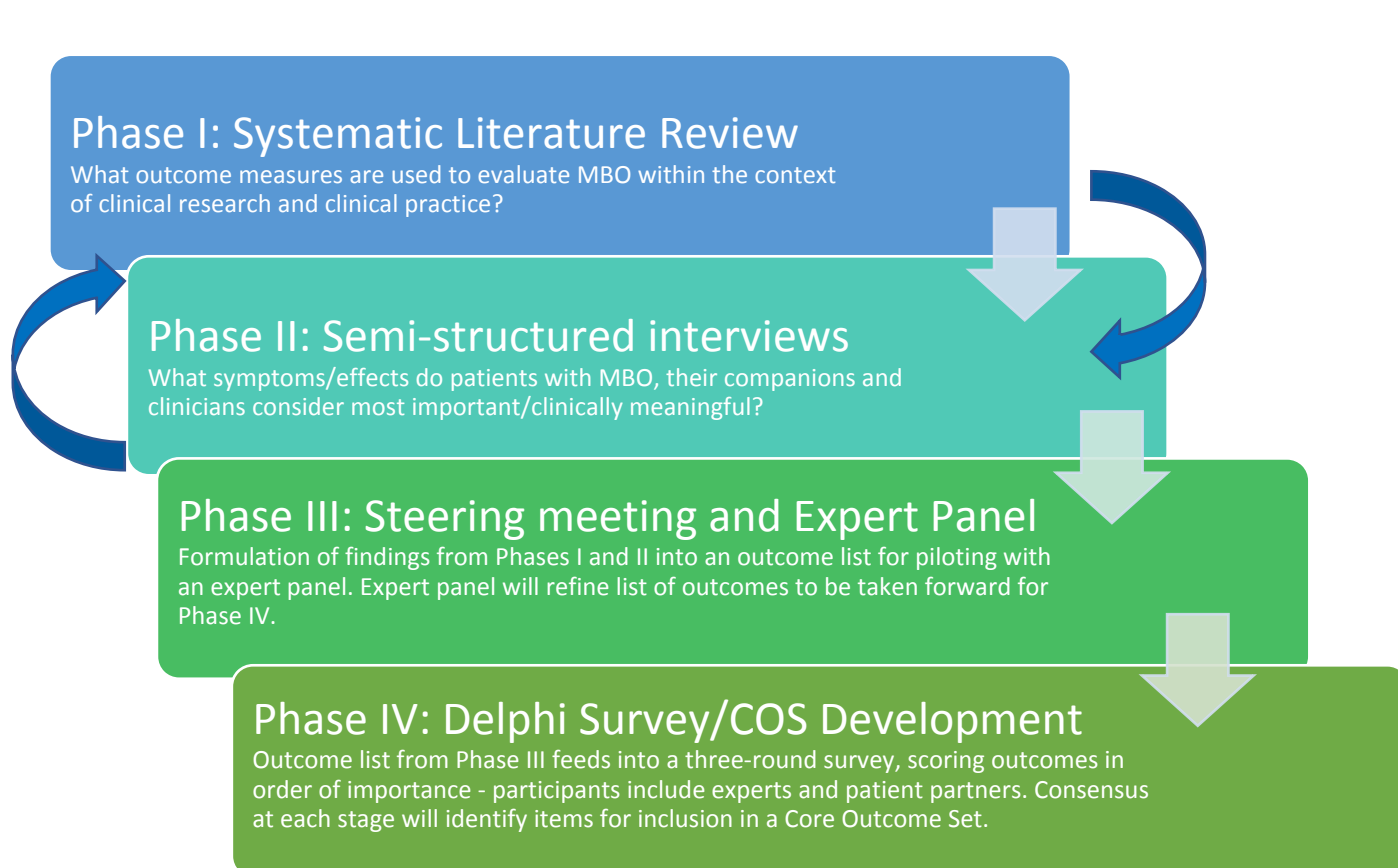
41 **Competing interests** The authors declare no competing interests.
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Fig. 1: Process for the development of a Core Outcome Set (COS) for Malignant Bowel Obstruction (MBO)

BMJ Open

Development of a Core Outcome Set to use in the Research and Assessment of Malignant Bowel Obstruction: protocol for the RAMBO study

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TITLE: Development of a Core Outcome Set to use in the Research and Assessment of Malignant Bowel Obstruction: protocol for the RAMBO study

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ABSTRACT

Introduction: Studies regarding the management of malignant bowel obstruction (MBO) report conflicting findings. This is partly due to different outcome measures being used to evaluate severity of MBO and the response to treatments. Furthermore, current outcome measures focus mainly on measurable physiological parameters which may not correlate strongly with patient-defined quality of life. The development of Core Outcome Sets allows a consistent approach to evaluating clinical conditions taking into consideration patient, health care professional and researcher viewpoints. It follows an internationally recognised standard methodology. We present a protocol for the development of a Core Outcome Set for Research and Assessment of Malignant Bowel Obstruction (RAMBO).

Methods: RAMBO is a multi-centre study, comprising of 4 phases: A systematic review to examine current scope of outcome measures associated with MBO (Phase 1). Interviews with patients, companions and health care professionals will explore priorities and preferences for care and outcomes (Phase 2). An expert panel meeting will collate the findings into a set of outcomes (Phase 3), refined by consensus through a Delphi survey with key stakeholders (Phase 4). The final set of outcomes will be ratified at a consensus meeting. Each step will actively include patient partners. Thematic analysis and descriptive statistics will be used to analyse qualitative and quantitative data respectively.

Ethics and dissemination: Ethical approval was obtained (Wales REC 5, REF: 19/LO/1876). Study participants and relevant stakeholders will be updated with newsletters and a lay summary at the end of the study. Abstracts will be submitted to national and international conferences, results papers will be submitted to peer reviewed, open access journals.

Study registration number: Core Outcome Measures in Effectiveness Trials (COMET) registration: 1402. Systematic Literature Review PROSPERO registration ID: CRD42019150648. Rapid Review PROSPERO registration ID: CRD42020176393

Strengths and limitations of the study

- This is the first study to develop a Core Outcome Set for the evaluation of malignant bowel obstruction.
- The protocol follows a well-established process following COMET guidelines, including a thorough systematic review, qualitative rapid review, semi-structured interviews with patients, their companions and healthcare professionals, followed by a three-step Delphi survey.
- The study outcomes will reflect what is important to patients and their companion/carers, as well as clinicians and researchers.
- Patient partner involvement (PPI) for this study adheres to the UK PPI standards and has occurred from the inception of the study, particularly the methodology, including data collection tools for patient and companion interviews.

- Since the qualitative data collection will occur in the United Kingdom, there may be limitations on how applicable the outcome measures will be if applied internationally.

Introduction

Malignant bowel obstruction (MBO) is bowel obstruction due to cancer or its treatments. It primarily affects people with advanced ovarian (10%-50%) and gastrointestinal cancers (15%) and remains a challenging condition facing oncology, surgical, gynaecology, gastroenterology and palliative care teams[1,2]. It is one of the most distressing complications of cancer, causing nausea, vomiting, abdominal distension, colic, pain and constipation[3-8]. It also has a persistent and profound effect on quality of life[9], and often requires hospitalisation for persistent unresolved symptoms[3].

Management options for MBO in patients with advanced cancer are limited; some, usually those with a single level bowel obstruction, may be offered surgery to resect an isolated tumour or create a de-functioning stoma. Some people may benefit from the endoscopic placement of a stent for palliative purposes. However, the majority of cases present with multiple level obstructions which are not amenable to surgical or endoscopic interventions. Pharmacological approaches for symptom reduction in inoperable MBO (IMBO) usually involve a combination of antiemetics and parenteral anti-secretory agents (anticholinergics, somatostatin analogues and H₂ antagonists), often with gut decompression (nasogastric tube or venting gastrostomy)[10-11].

Current evidence informing the symptom management of IMBO is inadequate; clinical guidelines favour somatostatin analogues but recommendations have been based, largely, on case series and insufficiently powered clinical trials[9]. Recently, two adequately powered, well-conducted clinical trials demonstrated no objective benefit with one of them suggesting evidence of harm[4, 12]. Importantly, these two trials included a placebo arm to reflect the natural history of IMBO, which is largely unknown, except that spontaneous resolution with recurrence is common and, for many people, it appears that vomiting will generally lessen in frequency and volume with time. However, these trials do not appear to have impacted on subsequent guidelines or clinical recommendations[13-16]; although there are some data showing they have affected clinical practice[17].

A recent systematic review of somatostatin analogues, using objective tools to evaluate data quality, concluded that there was moderate evidence of no benefit, and only poor evidence for their use[18]. The authors suggested that the most significant challenge in evaluating current data lay with the many studies using differing clinical outcomes, thereby making it impossible to objectively compare study outcomes or submit them to meta-analysis. The lack of an agreed core outcome set (COS) for MBO

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3 has considerable challenges in ensuring consistent clinical and research evaluation of interventions
4 for patients with MBO.
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10 Identifying outcome measures that reflect real-world settings 11

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13 In order to ensure outcomes measures are relevant to patients, it is essential to have patients at the
14 frontline of the research in order to ascertain their quality of life and preferences for symptom
15 management and care. Patient reported outcomes (PROs), when collected and analysed
16 appropriately, are key to shared decision making, clinical guidelines and health policy[19]. Involving
17 patients' views and understanding the challenges they face are invaluable in understanding how care
18 happens in real world settings, otherwise trials might fail to account for the outcomes that matter
19 most to patients[20].
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28 Rationale of COS development for MBO 29

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31 A key issue identified on both a national and international level is the lack of data indicating how
32 primary outcome measures used to evaluate MBO relate to patient experience[1, 17]. For example,
33 measures of symptom relief may not directly reflect what is important to patients and their
34 companions (next of kin/carers), and what they consider to be meaningful[18].
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39 The broad and varied approaches to outcome measurement in the palliation of MBO, and the lack of
40 an evidence base for patient-relevant measures, has led to a diversity of approach in clinical trials and
41 inconsistent recommendations in clinical guidelines. Importantly, the continuation of poorly
42 evidenced clinical practice may also cause harm[21]. Recent publications have called for the
43 development of a COS, to ensure uniformity of symptom assessment within clinical trials and clinical
44 practice[21]. This study aims to address this gap. It will ascertain patients' perceptions of the
45 management of their condition, compare these with outcomes measured in the current literature,
46 and gain consensus on an agreed set of core outcomes to be used in clinical practice to streamline
47 appropriate and targeted management of MBO.
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Aims

The RAMBO study aims to review the current scope of outcome measures used to evaluate MBO and to develop a set of core outcomes specific to MBO. It will ask the following questions:

1. What outcome measures are currently used to evaluate MBO within the context of clinical research and clinical practice?
2. What symptoms and effects do patients with MBO, their companions and health care professionals consider most important, and what improvement would they consider clinically meaningful?
3. How do currently used outcomes map to those factors identified as important by patients, their companions and health care professionals, and what are the gaps and limitations in current measures?

Methods

Study design

We propose to use a multi-phase, mixed-method, multi-centre study to address the research questions. In Phase I, a systematic literature review will be conducted to identify outcomes currently used to evaluate MBO. Phase II will comprise of interviews with patients, their companions and health care professionals to understand their experiences, priorities and preferences for care. The findings of these two phases will inform Phase III, an expert panel meeting, to direct the compilation of a comprehensive list of outcomes which will feed into the Phase IV Delphi survey, a two-round ranking exercise followed by a consensus meeting. The aim of the Delphi is to achieve consensus on a final COS. A summary of the design can be seen in Figure 1. Dissemination will follow the Core Outcome Set-STAndards for Reporting (COS-STAR) Statement[22].

PPI – Patient and Public Involvement

We actively support the fundamental involvement of patient and public involvement (PPI) as set out by the UK Standards for Public Involvement in research in all of our research[23]. The RAMBO study has recruited two research partners (one of which is a co-applicant on the study) to represent lay stakeholders in the study management group advising on recruitment and participant-facing documentation. They will also contribute to thematic analysis of the interview data. Lay representatives will also be involved in the interpretation and dissemination of study results.

Phase I: Systematic Literature Review

The COMET Initiative recommends a systematic literature review (SLR) as an initial phase in studies developing COS [22]. This will identify all outcomes used in clinical trials and observational studies in patients undergoing palliative treatment for inoperable MBO. Qualitative papers will not be included as they do not quantify outcomes, but a separate, rapid review of qualitative studies will inform the writing up of the Phase II interview study (see below). Databases to be searched include MEDLINE, EMBASE, CINAHL, CareSearch and the Cochrane Central Register of Controlled Trials (CENTRAL). Other sources will include reference lists of included articles and of previous systematic reviews of MBO interventions, conference proceedings, grey literature, and the authors' own files. No date or language restrictions will be imposed.

The research questions that the review seeks to answer are:

- What outcome measures are used to evaluate clinical, symptomatic and psychological aspects of malignant bowel obstruction (MBO) within the context of clinical research and practice?
- How is the timing of outcome measures justified?
- Which outcome measures should be considered for inclusion in a COS for future clinical trials?

A broad range of study designs and heterogeneous data are anticipated in papers meeting the inclusion criteria for this review, and data will be explored using narrative synthesis. The review will record all clinical, symptomatic and psychological outcomes reported in included studies, with the

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3 definitions and time points of each measure, and review their heterogeneity and their relevance to
4 patients with MBO. Data will be extracted and grouped with reference to the outcomes taxonomy
5 recommended by COMET. The full protocol for the review, including the search strategy and study
6 selection criteria, is available on the PROSPERO database, ID: [CRD42019150648](https://doi.org/10.1136/201901150648).
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10 11 12 Phase II: Interviews with patients, their companions and health care 13 professionals 14 15

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22 Interviews will explore the experiences of approximately 15 patients with MBO, what outcomes they
23 would most value from their care, and the experiences of their companion if possible. In this case,
24 companion if defined as a significant informal carer or family member (aged over 18). Patients eligible
25 for interview will be adults aged 18 or over with histologically confirmed cancer, with their MBO
26 currently or recently resolved but with risk of recurrence, as confirmed by either two senior medical
27 practitioners or one medical practitioner in combination with confirmatory radiology. Patients will be
28 interviewed with their carer/companion present if this is the patient's preference; carers/companions
29 will be interviewed separately where this is preferred. We will not include patients who have any
30 diagnosed medical problems that would prohibit them from participating in a 30-minute to 1-hour
31 interview.
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36 We will also interview approximately 15 healthcare professionals from a breadth of clinical specialties
37 involved in the care of patients with MBO at the recruitment sites in the 12 months previous to
38 recruitment, to explore the experiences involved in the management of MBO. Healthcare
39 professionals will be purposively sampled to ensure a breadth of clinical specialties involved in the
40 management of MBO, including primary care, palliative care, oncology, colorectal and gynaecological
41 surgery.
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46 The sample size of participants is based on past experience of patients receiving palliative care services
47 across multiple studies and aims to reach data saturation – the point at which no new topics emerge.
48 This will be achieved by constant re-evaluation and discussion between the two interviewers and with
49 input from the study management team.
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Data collection

A semi-structured interview format will be used to explore patients' understanding, experiences and symptoms of MBO, what matters most to patients with MBO, and what they consider to be a meaningful improvement regarding the relief of MBO symptoms. Interviews conducted with healthcare professionals will explore their experiences of managing MBO, how they evaluate severity and symptomatic response to treatment, what they perceive matters most to patients in regards to treatment of MBO, and how they perceive 'meaningful improvement' in a patient with MBO.

Interviews are expected to last between 30 minutes and 1 hour. They will be undertaken in a quiet location at participating hospitals or hospices or an alternative location of the participants' choice, at a time specified by the participant.

Interviews will be audio recorded on an encrypted recording device (with the participants' consent) and uploaded onto a secure server, labelled with an identifying code, with no reference to personal details. Audio files will be transcribed verbatim by an authorised agency. Basic demographic data will be collected and reported descriptively but not used as sampling criteria. Transcripts will be checked to ensure anonymisation by a member of the research team before being uploaded to NVivo12[24] qualitative software for data management.

Consent

Written consent will be obtained at the outset of each interview. Individuals that lack the capacity to consent will not be included in this study. Participant information sheets will be distributed to potential participants by their clinical team, to give participants the time to make an informed decision whether or not they wish to participate. If they choose to participate, they will inform a member of their clinical team, who will pass on the patients' contact details to the researcher or the patient can contact the researcher directly. The researcher will take written consent before the interview commences; participants will have the chance to ask questions before the interview, and it will be stressed to the participant that they are under no obligation to take part and may withdraw from the study at any point during the interview, and that their participation has no influence on their medical care.

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3 Healthcare professionals will be invited by email to participate in the study, with a follow-up email
4 after one week; eligible participants will be identified by the Clinical team, and the email will provide
5 them with a participant information sheet. If a potential participant expresses interest, they will be
6 asked to contact the researcher directly, or asked permission for the researcher to contact them. An
7 interview slot will be arranged at an appropriate time for the individual and written consent will be
8 taken by the researcher.
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17 Data Analysis

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21 Thematic analysis[25] will be used to interrogate the interview data. Analysis will be conducted by two
22 researchers, with experience in qualitative research, but no fixed views regarding the management or
23 assessment of MBO. After an initial period of independent coding, meetings will be held between the
24 two researchers to refine the themes and their concomitant categories. The analysis framework will
25 be iteratively refined until all transcripts have been coded and a final thematic framework
26 produced[25].
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32 Findings from Phase I (systematic literature review) and Phase II (interviews) will be summarised in a
33 report which addresses the main research question: What issues do patients, their companions and
34 health care professionals consider to be most important in the management of symptoms of MBO,
35 and what improvements would they consider meaningful? These data will also be synthesized with
36 the qualitative data (Phase II interviews) identified through a rapid review of the qualitative literature.
37 The report will seek to identify significant experiences and priorities among patients, their carers (if
38 present) and health care professionals, that align with measurable outcomes[23] and can be taken
39 forward into the initial outcomes list presented in Phase III.
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49 Phase III: Steering Meeting and Expert Panel

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52 A steering meeting will be held to consolidate the findings of the SLR and interview study, to produce
53 a list of outcomes to be taken forward into Round 1 of the Delphi. The outcome list will be discussed
54 and refined by an Expert Panel (consisting of approximately 10 academics/patient or carer research
55 partners/healthcare professionals chosen for their recognised expertise in and/or experience of
56 MBO), following CREDES guidelines for the Delphi technique[26].
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Phase IV: Delphi Survey

The Delphi survey will be carried out using Online Survey UK, an electronic bespoke survey format which has previously been developed by the COMET Initiative for the use in COS development projects. A piloting round will be conducted with expert and lay members of the steering panel prior to wider stakeholder involvement. If issues needing resolution arise from this process, a second pilot round will be included. The survey will present the list of outcomes to stakeholders in two rounds, with a final Consensus Meeting to resolve points of difference. The aim of the process is to reach consensus, taking in a range of viewpoints: stakeholders will include patient representatives and health care professionals in the area of clinical oncology, colorectal surgery, gastroenterology, gynaecological surgery and specialist nursing. Anonymous results from the first round will be circulated between all stakeholder groups as a basis for the subsequent round of decision-making. Items on which the agreed threshold of consensus is reached in round one will be dropped from round two. This technique is recognised by the COMET Initiative as appropriate to the development of COS[23, 27].

Recruitment

Identification of potential patient research partners will take place in tandem with recruitment for Phase II of the study, via the same recruitment channels, and through formal carer or bereavement groups run by voluntary organisations. Healthcare professionals will be recruited from hospitals and hospices, and by using the authors' professional networks. Participants will be recruited through telephone, email or post. No new participants will be invited following the completion of Round 1.

Based on recruitment numbers in previous studies and a pragmatic approach to reaching consensus[28-29], we will aim to recruit a minimum of 40 respondents to take part, including patients/companions, health care professionals and policy. Consent will be implicit through the participants' registration to take part and completion of the survey. Each participant will be represented in the survey documents by a unique identifier label; personal details will be kept confidential in a separate database on secure on-line storage.

Delphi Process

The outcome list produced during Phase III will be used to construct the Delphi survey. Panel members will be asked to score each outcome on a Likert scale ranging from 1 to 9[27] (1-3 – limited importance, 4-6 – important, 7-9 – critically important), relative to the other outcomes, in terms of the following question:

- Please consider each listed outcome, and rate how important it is to measure a change in the outcome when providing palliative care to address the symptoms of malignant bowel obstruction?

In addition to scoring outcomes, free text boxes will allow comments to be gathered on each item in each round of the survey, to make decision-making visible and assist other participants to refine their decision-making in the following round. This will allow respondents to add additional outcomes in order to address any perceived gaps in the way that patients' experiences are measured.

We anticipate two rounds to refine and rank outcomes in order to reach consensus, followed by a Consensus Meeting to resolve any items on which agreement is not reached. For each outcome in each round, the distribution of scores will be summarised, and items scored as of limited importance by all respondents will be dropped from subsequent rounds; all other items will be carried forward. The pre-set agreement criterion for scoring outcomes at each stage will be $\geq 70\%$, based on previous studies describing the development of COS[30-31]. Consensus will be reached if the majority of participants score a specific outcome similarly. Three categories will be assigned for each outcome:

- **Consensus: in** – 70% or more respondents within a stakeholder group rate the outcome as critically important, and 15% or fewer rate the outcome as of limited importance.
- **Consensus: out** – 70% or more of participants rated an outcome as of limited importance, and 15% or fewer rated the outcome as critically important.
- **No consensus** – none of the above criteria are met.

If 70 per cent or more of the respondents agree that an outcome is of low importance in Round 1, this item will be dropped from Round 2. If 70 per cent or more of respondents agree that an outcome is of high importance in Round 1, this item will be dropped from Round 2, and will be proposed for inclusion in the final core outcome set. All other items will be carried forward. In Round 2, participants will be shown the number of respondents and distribution of scores for each remaining outcome from

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3 all stakeholder groups, with their own score from Round 1. They will be asked to consider the
4 responses from other Delphi participants, and to re-score the items. If a participant changes their
5 score from of limited importance (<4 in Round 1) to critically important in Round 2 (7 or more) or from
6 critically important in Round 1 to of limited importance in Round 2, they will be asked to provide the
7 reason for this change. We will also examine any other changes in scores between rounds and
8 summarise reasons given for these changes.
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14 Items on which agreement was not reached will be discussed and resolved at the final Consensus
15 Meeting. Outcomes from the Delphi survey classed as 'consensus in' across all groups will be proposed
16 for inclusion in the final COS; outcomes classed as 'consensus out' will be proposed for exclusion.
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20 21 22 Consensus Meeting

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27 All Delphi participants will be eligible for inclusion in a face-to-face Consensus Meeting to achieve a
28 final recommendation of a core set of outcomes. The survey registration page for Round 1 will ask
29 participants to tick a box to allow the study team to approach them for inclusion. Appropriate
30 secondary stakeholder groups recommended by existing stakeholders will be invited to take part at
31 this stage. Written consent will be taken at the outset of the meeting from all participants to audio
32 record the discussion; the audio file will be transcribed and anonymised. Participants will discuss all
33 outcomes and their status at the close of the survey. They will then vote on an outcome-by-outcome
34 basis to confirm consensus, or to suggest that an outcome requires further discussion. Further voting
35 rounds will be conducted as necessary until the final outcome set is agreed.
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46 Ethical Considerations

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48 Ethical approval for the study was obtained 10th December 2019, from Wales Research Ethics
49 Committee 5 Bangor (REF: 19/LO/1876). All data will be collected according to the principles of the
50 General Data Protection Regulations and Data Protection Act 2018[32].
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55 Dissemination

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58 The study is registered with the COMET database and dissemination through this will complement
59 peer review publications. Study participants and relevant bodies (e.g. health care professionals
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3 involved in the management of MBO – including palliative care, gynaecology and colorectal surgery
4 and patient partner organisations) will be regularly updated with newsletters and a lay summary at
5 the end of the study. We will disseminate the research findings widely. Abstracts will be submitted to
6 national and international conferences, results papers will be to relevant stakeholders at international
7 conferences and submitted to publish in high impact, open access journals. Dissemination will be
8 undertaken with professional organisations such as the Association of Palliative Medicine (APM),
9 European Association for Palliative Care (EAPC), The Multinational Association of Supportive Care in
10 Cancer (MASCC), The American Society of Clinical Oncology (ASCO), The European Society for Medical
11 Oncology (ESMO), National Cancer Research Institute (NCRI) and Hospice UK to adopt the
12 recommendations from the work. Lay summaries will be uploaded on the Marie Curie website,
13 including on the MCPCRC specific website and Wolfson Palliative Care Research Centre (WPCRC)
14 websites, and sent to key PPI groups and disseminated via social media.
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41 **Contribution** JB, SN, MJ, DC, FM, EBD*, GO, KS and AN contributed equally to the development of the
42 study, and writing of the protocol. EB* and AB wrote the first draft of the manuscript. EB, AB, JB,SN,
43 MJ, DC, FM, EBD, GO, KS, AO and AN contributed to the refinement of the manuscript with specific
44 additional contributions as follows: clinical overview and research methodology (JB,SN, MJ, DC, FM,
45 EBD, GO), systematic review (GO, JB), qualitative research (AN), PPI including interview schedules and
46 participant information. JB and SN maintained oversight of the manuscript and are chief investigators
47 of the study.
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52 *EB – Elin Baddeley, EBD – Elaine Boland
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59 **Competing interests** The authors declare no competing interests.
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Figure Legend(s) *Figure 1: Process for the development of a Core Outcome Set (COS) for Malignant Bowel Obstruction (MBO)*

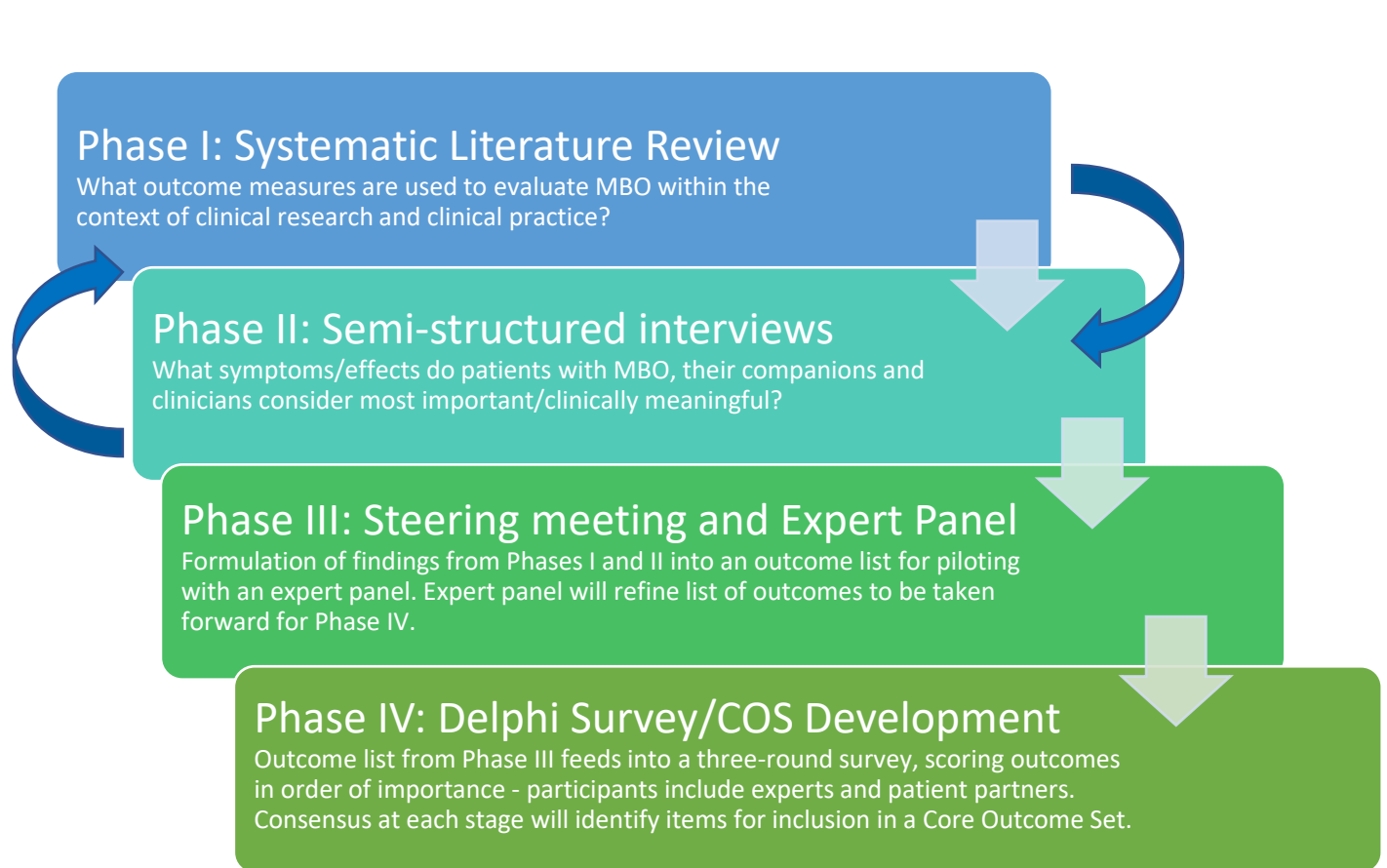
For peer review only

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29 *Fig. 1: Process for the development of a Core Outcome Set (COS) for Malignant Bowel Obstruction (MBO)*