**A core outcome set for localised prostate cancer effectiveness trials**

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# Introduction

Treatments for localised prostate cancer can be associated with side effects such as urinary incontinence, erectile dysfunction or bowel dysfunction. These may be permanent and cause significant impairment of quality of life. (1) The choice between treatments is driven by the therapeutic ratio with a balance between cancer control and the likelihood of experiencing adverse events, speed of return to routine activities and long-term impact on health-related quality of life. (2, 3)

It is therefore critical that outcomes important to all stakeholders are measured and reported. However, many systematic reviews of effectiveness (4-9) and clinical practice guidelines (10) acknowledge the difficulties in synthesising the evidence base due to heterogeneity in outcome selection, definitions, measurement and reporting across different trials.

A potential solution is a “core outcome set” (COS), which is a minimum set of outcomes that should be measured and reported in effectiveness trials in a particular condition. (11) Its use can reduce heterogeneity in outcome selection, measurement and reporting across trials, and facilitate evidence synthesis. (12, 13)

A ‘standard set of patient-centred’ outcomes was developed by Martin et al (14). However, Martin et al’s purpose was to provide quality indicators for institutional registries, “outside of clinical trials” (15) with which clinicians or hospitals may measure themselves competitively to “drive competition around value”. As such, their work was not a COS for effectiveness trials. (14) Furthermore, the inclusion of only two patients in Martin et al’s consensus process is unlikely to be sufficient and may have biased any results toward clinician preference. (16) Lastly, the tools used to measure their standard set were not evaluated transparently or robustly with regards to measurement properties and feasibility. (13) It is currently unclear which measures should be used in the outcomes measured in clinical trials.

We report here the results of the development and establishment of a COS for *intervention* *effectiveness trials* for localised prostate cancer. The intention was to identify core outcomes which were applicable across all intervention and outcomes which may be intervention-specific. The scope of the project led to the appropriate methods (outlined below) which are advocated by the COMET initiative, (11, 12) and are explained further in our study protocol. (17) We report our study in line with the COS-STAR reporting guidance. (18)

## 1.2 Aims and objectives

The aim was to establish a COS for trials of primary interventions for localised prostate cancer (defined as clinical TNM stage ≤T2N0M0) (19) which is applicable across all interventions, including adjuvant hormonal therapy.

Specific objectives were to:

1. Achieve consensus amongst patients and healthcare professionals on outcomes critically important to decision-making; and
2. Establish a COS for use in future trials assessing interventions for localised prostate cancer.

# Materials and Methods

## 2.1 Protocol registration and ethical approval

The methodology used was that recommended by the COMET Initiative – the international expert body dedicated to the robust development of COS. (20) The study protocol was published (17) and the study approved by the National Research Ethics Service (NRES) – North of Scotland Committee (reference 12/NS0042). A project steering committee was established to provide oversight.

## Achieving consensus amongst patients and healthcare professionals on critically important outcomes

The consensus building process was divided into two phases: (1) Delphi survey involving prostate cancer patients in the UK, and healthcare professionals (HCPs) involved in the management of localised prostate cancer across the UK, Europe and the USA; and (2) formal consensus group meeting involving patients and HCPs.

## Delphi survey

Delphi surveys are a well-recognised and increasingly-used consensus method for COS development. (21) A systematic review of the literature was initially performed to ascertain the full range of outcomes that had previously been reported in trials of interventions for localised prostate cancer. (22) In addition, semi-structured interviews were conducted with a purposive sample of patients to identify any further potentially relevant outcomes. (22) All identified outcomes where entered into a bespoke online Delphi tool, written in C# using WebForms and a MySQL backend. The full list of outcomes included in the questionnaire (and their definitions) is shown in Appendix 1. Survey participants rated each of the items’ importance for decision-making.

Patients and HCPs were chosen because they are important stakeholders in the management of localised prostate cancer. Participants from the UK were primarily targeted due to feasibility and resource issues. Patients were eligible if they had been treated or managed for localised prostate cancer and were identified through the UK-based UCAN charity’s prospective patient database (23) and through prostate cancer support groups registered in the UK and listed on the National Federation of Prostate Cancer Support Groups’ website. (24) HCPs were identified through the following membership directories and websites: British Association of Urological Surgeons (BAUS), British Association of Urological Nurses (BAUN), European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), European Association of Urology Guidelines Office, and the Cochrane Urology group. Purposive sampling was undertaken, covering different treatments, age and time since treatment for patients, and type of HCP (urologist, oncologist, or cancer nurse specialist) and area of expertise (robotic or laparoscopic radical prostatectomy, ablative therapy, external beam radiotherapy, brachytherapy, and active surveillance). 153 patients and 110 HCPs were invited, with an anticipated completion rate of 50%. Informed consent was presumed if participants registered to take part in the online survey.

The questionnaires and participant information sheets were assessed for face validity in a focus group with 6 patients and 5 HCPs. Three iterative rounds were planned, and after round one, participants were reminded of their own scores and provided with feedback from within their own groups and/or from the other groups. Participants had the opportunity to revise their score, or add further items into the survey for incorporation in the following round. No items were dropped between rounds. Participants were asked to score the importance of each outcome listed on a 9-point scale adapted from GRADE (25) (i.e. 1-3 = not important; 4-6 = important; 7-9 = critical; together with an ‘unable to score’ option).

Descriptive statistics were used to summarise the results of each round, including the percentage of participants scoring each of 1-9 for the outcome. The results for each stakeholder group were analysed and presented separately in each round. After the final round, items scored as critical (i.e. 7-9) by ≥70% of patients and HCPs separately AND not important (i.e. 1-3) by <15% of patients and HCPs separately were eligible for inclusion in a preliminary core outcome set (i.e. ‘consensus in’ outcomes). Conversely, items scored as not important (i.e. 1-3) by ≥70% of patients and HCPs separately and critical (7-9) by <15% of patients and HCPs separately were excluded from further analysis (i.e. ‘consensus out’ outcomes). All other outcomes were classified as ‘equivocal’. These scoring thresholds were based prior COS projects. (26-28) All outcomes were available for discussion and voted on at the consensus group meeting.

## Consensus group meeting

A one-day consensus group meeting was held to review the preliminary COS derived from the Delphi survey, and to discuss, deliberate and vote in order to establish the final COS. Patients and HCPs were purposively sampled from those completing all rounds of the Delphi survey to ensure representation of patients receiving the range of treatment types, and urologists, oncologists and cancer nurse specialists. Non-voting observers, a patient and public involvement coordinator (PPI), and non-clinical members of the project steering group also attended. The meeting was chaired by a member of the Steering Group [PRW].

Voting was undertaken anonymously using personalised electronic handsets. (29) All items were individually presented, reviewed, discussed and voted upon regarding their importance for decision-making. Participants were asked “Is this outcome important enough to be included in the COS?” and asked to score the outcomes on the same 1-9 scale as the Delphi survey. Items scored as critical (i.e. 7-9) by ≥70% and not important (i.e. 1-3) by <15% of voting members were eligible for inclusion in the final COS. The results for an outcome were conveyed to participants immediately after voting, and the final COS was shown to all participants at the end of the meeting.

# Results

## An overview of the COS development process and summary of results can be seen in Figure 1.

## 3.1 Consensus amongst patients and healthcare professionals on critically important outcomes

## Delphi survey

The systematic review and patient interviews generated 79 discrete outcomes which were incorporated into an online questionnaire (Appendix 1). A total of 152 participants completed all 3 rounds of the survey. Of these, 47 (31%) were HCPs and 105 (69%) were patients. The completion rate (i.e. proportion who completed all 3 rounds of the survey out of those invited) was 43% for HCPs and 69% for patients. The overall attrition rate (i.e. drop outs between rounds 1 and 3) was 13%. We investigated whether attrition may have introduced bias by comparing the mean (SD) round 1 scores for those completing round 1 and round 2 (5.9 (1.3)) with those who dropped out after round 1 (5.8 (1.5)). We then repeated this for mean (SD) round 2 scores for those completing round 2 and 3 (6 (1.2)), compared with those who dropped out after round 2 (5.7 (0.7)). Those dropping out between rounds did not appear to hold different views, suggesting that there was no attrition bias.

Tables 1a and 1b summarise the treatment/expertise characteristics of the patients and HCPs who completed all 3 rounds of the survey. In addition, the detailed characteristics of HCPs completing all 3 rounds are included in Appendix 2. Five additional outcomes were proposed by participants in round 1 (impact on relationship with partner, bladder pain, urinary tract infection, induction of new cancers, and side effects of hormonal therapy), and these were incorporated into subsequent rounds. Table 2 summarises the results from Delphi survey round three, showing how each outcome was finally scored by patients and HCPs with the results expressed as proportions for each category of ‘not important’, ‘important’, and ‘critical’, for the entire study cohort. The outcomes which fulfilled the criteria for ‘consensus in’, and ‘equivocal’ outcomes are indicated. No outcomes met the criteria for ‘consensus out’.

## Consensus group meeting

The consensus group meeting was held at the University of Aberdeen, Scotland on the 22nd February 2016. A total of 21 voting members attended (8 patients, 13 HCPs). The list of participants along with their expertise is given in Table 3. For patients, the median [IQR] time since treatment was 3.5 [2.6-4.3] years. The complete results of the Delphi survey were presented and discussed.

Following discussion, four outcomes (urinary function, bowel function, sexual function and overall quality of life) were grouped back into broader domains. This was done because there was a split vote i.e. that everyone voted some aspect of those domains as critical (7-9) but not all voted for the same aspect. Consequently, this was a pragmatic means of taking into account the heterogeneity of responses from the Delphi survey and consensus meeting in regard to those discrete outcomes Therefore, these multi-dimensional outcomes will need careful consideration of appropriate measurement instruments – which is part of the planned future research. The original categories for urinary function, bowel function, sexual function and overall quality of life outcomes before re-categorisation can be viewed in Appendix 1.

The results of the voting for each outcome are summarised in Appendix 3. The final core outcome set is summarised in Table 4, along with the interventions each core outcome is relevant to. The final COS contains 19 outcomes, with 12 universal outcomes (i.e. relevant across all interventions) and 7 intervention-specific ones (4 for surgery, and one each for active surveillance, cryotherapy/HIFU/ablative therapy, and hormonal therapy).

# Discussion

Our study adopted robust methods to generate a core outcome set relevant to trials of interventions for localised prostate cancer. From the consensus process, 19 core outcomes were identified: 12 universal and 7 intervention-specific, covering all domains of cancer control and survival, urinary function, bowel function, sexual function, quality of life, and adverse events.

There have been two recent reports on developing standardised outcomes in the field of localised prostate cancer. Martin et al. (14) defined a set of health outcomes for localised prostate cancer management, to be measured in routine clinical practice with the purpose of determining the value of health care interventions; (14) and van den Bos et al. (30) reported on a consensus statement regarding the design of future trials of focal ablative therapy for a sub-set of patients with localised prostate cancer. Additional insights provided by our study are that it is the first localised prostate cancer study that takes into account the opinions of patients on a large scale and uses robust and transparent methods planned *a priori*.

Whilst it is encouraging that there is broad overlap between Martin et al’s outcomes recommended for clinical practice and our COS for effectiveness trials, it is important to reiterate the differences in the aims of the two studies, i.e. we aimed to develop a COS for effectiveness trails, Martin et al’s standard-set was not designed for trials but for routine clinical practice. It is important also to re-state the methodological differences. In particular the involvement of only two patients in Martin et al’s consensus process is unlikely to sufficiently capture patient opinion. (15, 16, 31) Ultimately, it is desirable for routine clinical data and data from trials to be commensurable, particularly in situations where routine data (such as rare events) might be more reliably captured in long-term institutional databases as opposed to the trial setting.

Van den Bos et al’s recommended primary outcome measure (negative biopsy at 12 months after treatment) (30) is encompassed within our outcome of treatment failure for ablative therapy in our COS. There are important differences between this study and our COS study. First, our COS study had a broader scope encompassing all current treatments for localised prostate cancer rather than a single type of intervention for a subset of patients with certain disease characteristics. Also, their expert group had no patient representation; the Delphi process does not give adequate information to assess how information was fed back to participants between rounds, and may have influenced subsequent rounds; and it is unclear how consensus was reached in the final meeting. (32)

This study is the most rigorous and largest of its kind, involving a large sample of patients from the UK, and HCPs from the UK, Europe and USA, producing a COS specifically developed for localised prostate cancer intervention trials using rigorous, protocol-driven, transparent and reproducible methods. (17) A comprehensive and robust systematic review to explore, define and characterise the nature of heterogeneity of outcome selection, definition and measurement was performed prior to a consensus-based process involving a Delphi survey and a consensus group meeting. The study involved a large, purposively sampled group of participants which included men with localised prostate cancer, and a diverse group of healthcare professionals from the UK, Europe and the USA. The Delphi survey included three iterative rounds, whereby feedback on others’ opinions was provided to allow participants to reflect, and to revise or maintain their responses as required, in addition to proposing any additional outcomes.

A limitation of the COS is that most of the participants were from the UK. However, we think that people in other countries should look at this well-developed COS and ask the question ‘Is there a reason why these results would not be similar to those that could be obtained in our population?’ If the answer is yes, then clearly more work is needed, but the default position should not be that a COS developed in one country will automatically not be applicable elsewhere. Additionally, more surgeons completed the survey and participated in the consensus meeting than oncologists. However, the HCP group also consisted of specialist nurses who provided crucially important perspectives regarding treatment with radiotherapy.

We assumed that most potentially important outcomes were likely to be reported in studies representing the highest levels of evidence only, based on the hierarchy of evidence, (33) on the basis that such studies are more likely to guide or change practice, and more likely to measure outcomes using validated tools. Although this may be considered a strength, it can also be regarded as a limitation because some potentially important outcomes may have been missed from our review. However, this risk is minimised by supplementing the long list of potentially important outcomes with additional outcomes identified from the semi-structured patient interviews, and from the Delphi survey where additional outcomes could be added.

The problems and issues arising from inconsistency and heterogeneity of outcome selection, definition, measurement and reporting in primary and secondary studies of localised prostate cancer are well documented. (4, 5, 7, 34, 35) Prospective trials of interventions for localised prostate cancer, should consider adopting the COS. Using our COS, future trialists have an opportunity to omit other outcomes which are not ‘core’, thereby reducing the burden on trialists, patients and funders. Some steps have been directed toward the implementation of the COS inasmuch as the COS is listed in the COMET database and COMET is targeting trial funders (e.g. NIHR guidance) and trialists (e.g. SPIRIT guidelines) to use COS, where they exist for planned trials.

Additional outcomes beyond the COS proposed (e.g. economic outcomes, related to use of health services, or specific surgical outcomes such as blood loss or anastomotic leak) might need to be measured to address questions beyond relative effectiveness, as these outcomes may be determinants of the cost and effectiveness components of a cost-effectiveness analysis.(36) There is also a valid argument for adopting the COS in clinical practice, since it reflects outcomes of greatest importance to patients and HCPs in making healthcare decisions. There is evidence that COS for trials align very closely with those required for informed consent (37).

Future work should focus on how the COS should be defined and measured in practice, incorporating elements such as standardising outcome definitions and thresholds, identifying the most appropriate measurement instruments, and time points for outcome assessment. We plan to address this in the next phase of our project, based on a strategy of appraising existing outcome measurement tools using objective criteria, such as those outlined in the OMERACT filter (36) or recommended by COSMIN. (13)

In conclusion, our study reports on the robust development of a comprehensive core outcome set for use in trials assessing interventions for localised prostate cancer. The final core outcome set includes 19 core outcomes, with 12 universal and 7 intervention-specific. The routine adoption of this COS in future trials of interventions for localised prostate cancer should ensure that outcomes of importance to patients and healthcare professionals will be collected and thus facilitate comparisons across different studies to allow informed treatment choices for patients, health care professionals and service providers.

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