DR. STEVEN MACLENNAN (Orcid ID : 0000-0002-2691-8421)

Received Date : 01-Feb-2017

Revised Date : 08-Mar-2017

Accepted Date : 20-Mar-2017

Article type : Original Article

A core outcome set for localised prostate cancer effectiveness trials

Steven MacLennan[1*], Paula R Williamson[2], Hanneke Bekema[3], Marion Campbell[4], Craig Ramsay[4], James N'Dow[1, 5], Sara MacLennan[1], Luke Vale[6], Philipp Dahm[14], Nicolas Mottet[23] and Thomas Lam[1, 5] on behalf of the COMPACTERS study group: Paul Abel[7], Hashim U. Ahmed[8], Gary Akehurst[9], Robert Almquist[9], Karl Beck[9], David Budd[9], Steven Canfield[10], James Catto[11], Philip Cornford[12], William Cross[13], Alexander Ewen[9], Judith Grant[15], Rakesh Heer[16], David Hurst[9], Rob Jones[17], Roger Kockelbergh[18], Andrew Mackie[9], Graham MacDonald[15], Alan McNeill[19], Malcolm Mason[20], Sam McClinton[5], Duncan McLaren[21], Hugh Mostafid[22], Ian Pearce[24], Linda Pennet[5], Justine Royle[5], Hans Schreuder[9], Grant D. Stewart[25], Henk van der Poel[26], Kevin Wardlaw[5], Thomas Wiegel[27],

*Corresponding author: steven.maclennan@abdn.ac.uk

1 Academic Urology Unit, University of Aberdeen, Aberdeen, UK

2 Department of Biostatistics, University of Liverpool, Crown Street, Liverpool, UK

3 Department of Anaesthesiology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

4 Health Services Research Unit, University of Aberdeen, Aberdeen, UK

5 Department of Urology, Aberdeen Royal Infirmary, Aberdeen, UK

6 Health Economics Group, Institute of Health and Society, University of Newcastle, Newcastle, UK

7 Faculty of Medicine, Department of Surgery & Cancer, Imperial College London, London, UK

8 Division of Surgery and Interventional Science, University College London, London, UK; Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK

9 Patient representative

10 Division of Urology, University of Texas Medical School at Houston, Houston, Texas, USA

11 University of Sheffield Academic Urology Unit and Academic Unit of Molecular Oncology, CR-UK/YCR, Sheffield Cancer Research Centre, University of Sheffield Medical School, Sheffield, UK

12 Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool, UK

13 St James's Hospital Institute of Oncology, Leeds, UK

14 Department of Urology, University of Minnesota, Minneapolis, MN, and Minneapolis VA Health Care System, Minneapolis, MN, USA

15 Department of Clinical Oncology, Aberdeen Royal Infirmary, Aberdeen, UK

16 Newcastle University and Freeman Hospital, Newcastle, UK

17 University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK

18 Department of Urology, University Hospitals Leicester, Leicester, UK

19 Department of Urology, Western General Hospital, Lothian University Hospitals, Edinburgh, UK

20 Velindre Hospital, Cardiff, UK

21 Department of Clinical Oncology, Western General Hospital, Edinburgh, UK

22 The Royal Surrey County Hospital, Guildford, Surrey, UK

23 Department of Urology, University Hospital, St. Etienne, France

24 Urology Department, Central Manchester University Hospitals , Manchester, UK

25 Academic Urology Group, University of Cambridge, Addenbrooke's Hospital, Cambridge Biomedical Campus, Cambridge, UK

26 Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands

27 Academic Urology Unit, University of Aberdeen, Aberdeen, UK

Objective: To develop a core outcome set (COS) applicable for effectiveness trials of all interventions for localised prostate cancer.

Background: Many treatments exist for localised prostate cancer, although it is unclear which offers the optimal therapeutic ratio. This is confounded by inconsistencies in the selection, definition, measurement and reporting of outcomes in clinical trials.

Subjects and methods: A list of 79 outcomes was derived from a systematic review of published localised prostate cancer effectiveness studies and semi-structured interviews with 15 prostate cancer patients. A two-stage consensus process involving 118 patients and 56 international healthcare professionals (HCPs) (cancer specialist nurses, urological surgeons and oncologists) was undertaken, consisting of a three-round Delphi survey followed by a face-to-face consensus panel meeting of 13 HCPs and 8 patients.

Results: The final COS included 19 outcomes. Twelve apply to all interventions: death from prostate cancer, death from any cause, local disease recurrence, distant disease recurrence/metastases, disease progression, need for salvage therapy, overall quality of life, stress urinary incontinence, urinary function, bowel function, faecal incontinence, sexual function. Seven were intervention-specific: perioperative deaths (surgery), positive surgical margin (surgery), thromboembolic disease (surgery), bothersome or symptomatic urethral or anastomotic stricture (surgery), need for curative treatment (active surveillance), treatment failure (ablative therapy), and side effects of hormonal therapy (hormone therapy). The UK-centric participants may limit the generalisability to other countries, but trialists should reason why the COS would not be applicable. The default position should not be that a COS developed in one country will automatically not be applicable elsewhere.

Conclusion: We have established a COS for trials of effectiveness in localised prostate cancer, applicable across all interventions which should be measured in all localised prostate cancer effectiveness trials.

1. 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.

2. 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.

2.2 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.

2.2.1 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.

2.2.2 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.

3. 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

3.1.1 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'.

3.1.2 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.

Acknowledgements

The authors wish to thank the following:

Heather Bagley and Linda Pennet for their advice and assistance regarding patient and public involvement in research; Janice Forsyth and Sarah Murdoch for their assistance with logistics before and during the consensus meeting; Melanie Harper-Jones and Duncan Appelbe for their support in designing and managing the online Delphi survey and data; Vikki Entwistle for her advice during the protocol development stage; and Jane Blazeby and Liz Gargon for providing advice on Delphi survey and consensus meeting methods. Finally, we would like to thank all patients and HCPs who took part in the interview study and Delphi survey.

References

1. Daskivich TJ, Lai J, Dick AW, Setodji CM, Hanley JM, Litwin MS, et al. Variation in treatment associated with life expectancy in a population-based cohort of men with early-stage prostate cancer. Cancer. 2014;120(23):3642-50.
2. Lotan Y, Cadeddu JA, Gettman MT. The new economics of radical prostatectomy: cost comparison of open, laparoscopic and robot assisted techniques. The Journal of urology. 2004;172(4 Pt 1):1431-5.
3. Zeliadt SB, Ramsey SD, Penson DF, Hall IJ, Ekwueme DU, Stroud L, et al. Why do men choose one treatment over another?: a review of patient decision making for localized prostate cancer. Cancer. 2006;106(9):1865-74.
4. Ip S, Dvorak T, Yu WW, Patel K, Obadan N, Chung M, et al. AHRQ Technology Assessments. Comparative Evaluation of Radiation Treatments for Clinically Localized Prostate Cancer: an Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010.
5. Ramsay CR, Adewuyi TE, Gray J, Hislop J, Shirley MD, Jayakody S, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess. 2015;19(49):1-490.
6. Hegarty J, Beirne PV, Walsh E, Comber H, Fitzgerald T, Wallace Kazer M. Radical prostatectomy versus watchful waiting for prostate cancer. 2010.
7. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. Annals of internal medicine. 2008;148(6):435-48.
8. Ollendorf DA HJ, McMahon P, et al. . Active surveillance and radical prostatectomy for clinically localized, low-risk prostate cancer.; 2009.
9. Ficarra V, Novara G, Artibani W, Cestari A, Galfano A, Graefen M, et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. European urology. 2009;55(5):1037-63.

10. Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol. 2007;177(6):2106-31.
11. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. J Health Serv Res Policy. 2012;17(1):1-2.
12. 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(1):1.
13. Prinsen CA, Vohra S, Rose MR, Boers M, Tugwell P, Clarke M, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline. Trials. 2016;17(1):449.
14. Martin NE, Massey L, Stowell C, Bangma C, Briganti A, Bill-Axelson A, et al. Defining a Standard Set of Patient-centered Outcomes for Men with Localized Prostate Cancer. European Urology. 2015;67(3):460-7.
15. Martin NE, Stowell C, Huland H. Reply to Steven MacLennan, Paula R. Williamson, and Thomas B. Lam's Letter to the Editor re: Neil E. Martin, Laura Massey, Caleb Stowell, et al. Defining a Standard Set of Patient-centered Outcomes for Men with Localized Prostate Cancer. Eur Urol 2015;67:460-7. Eur Urol. 2015;68(6):e125-6.
16. MacLennan S, Williamson PR, Lam TB. Re: Neil E. Martin, Laura Massey, Caleb Stowell, et al. Defining a Standard Set of Patient-centered Outcomes for Men with Localized Prostate Cancer. Eur Urol 2015;67:460–7. European Urology. 2016;68(6).
17. MacLennan S, Bekema HJ, Williamson PR, Campbell MK, Stewart F, MacLennan SJ, et al. A core outcome set for localised prostate cancer effectiveness trials: protocol for a systematic review of the literature and stakeholder involvement through interviews and a Delphi survey. Trials. 2015;16(1):76-.
18. 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.
19. Leslie H. Sobin (Editor) MKGE, Christian Wittekind (Editor). TNM Classification of Malignant Tumours, 7th Edition2009 November 2009, Wiley-Blackwell. 336 p.
20. COMET. Home: Core Outcome Measures in Effectiveness Trials Initiative (COMET) [Available from: http://www.comet-initiative.org/.
21. Gorst SL, Gargon E, Clarke M, Blazeby JM, Altman DG, Williamson PR. Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and User Survey. PLoS One. 2016;11(1):e0146444.
22. Maclennan SL, TBL. MacLennan, SJ. and N'Dow. J. Developing a core outcome set for localised prostate cancer effectivenes trials: Study outline and early results. COMET III; Pontificia Università Lateranense , Rome, Italy2014.
23. UCAN Urological Cancer Charity 2016 [Available from: http://www.ucanhelp.org.uk/.
24. NFPCwebsite. National Federation of Prostate Cancer Support Groups [Available from: http://www.tackleprostate.org/member-organisations.php.
25. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is “quality of evidence” and why is it important to clinicians? 2008.
26. Bruce I, Harman N, Williamson P, Tierney S, Callery P, Mohiuddin S, et al. The management of Otitis Media with Effusion in children with cleft palate (mOMEnt): a feasibility study and economic evaluation. 2015.
27. McNair AG, Whistance RN, Forsythe RO, Macefield R, Rees J, Pullyblank AM, et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. PLoS Med. 2016;13(8):e1002071.
28. Potter S, Holcombe C, Ward JA, Blazeby JM. Development of a core outcome set for research and audit studies in reconstructive breast surgery. The British journal of surgery. 2015;102(11):1360-71.
29. Banxia. Student response systems. 2016.

30. van den Bos W, Muller BG, de Bruin DM, de Castro Abreu AL, Chaussy C, Coleman JA, et al. Salvage ablative therapy in prostate cancer: international multidisciplinary consensus on trial design. Urol Oncol. 2015;33(11):495.e1-7.
31. Wittmann D, Skolarus TA. Re: Neil E. Martin, Laura Massey, Caleb Stowell, et al. Defining a Standard Set of Patient-centered Outcomes for Men with Localized Prostate Cancer. Eur Urol 2015;67:460-7. Eur Urol. 2016;69(6):e125-6.
32. Blazeby JM. Consistency in design and collaboration in delivery: key to successful randomised controlled trials in focal therapy for prostate cancer. Eur Urol. 2014;65(6):1084-5.
33. Bob Phillips CBDSDBSSBHMDsNUbJHM. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009) - CEBM.
34. Ramsay C, Pickard R, Robertson C, Close A, Vale L, Armstrong N. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. 2012;16(41).
35. Budaus L, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol. 2012;61(1):112-27.
36. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol. 2014;67(7):745-53.
37. McNair. A WR, Macefiled. R, Brookes. S, Blazeby. J. Do Patients want to know what Surgeons Tell Them before Colorectal Cancer Surgery? A Comparison of Surgeons' and Patients' Views of Important Information for Informed Consent. British Journal of Surgery: John Wiley & Sons, Ltd; 2016. p. 29.

Table 1a: Summary of characteristics of patients who completed all three rounds of the Delphi survey

Patients (N = 105)												
Age N (%)		**Primary treatment N (%)**					**Time since treatment N (%)**			**Country of origin N (%)**		
≤60 years	**>60 years**	**Surgery**	**EBRT**	**Brachytherapy**	**AS**	**Ablative therapy**	**≤1 year**	**2-5 years**	**>5 years**	**Scotland**	**England**	**Wales**
19 (18)	86 (82)	50 (48)	26 (25)	7 (7)	17 (16)	5 (5)	17 (16)	53 (51)	35 (33)	20 (19)	72 (69)	13 (12)

Table 1b: Summary of characteristics of HCPs who completed all three rounds of the Delphi survey

HCPs (N = 47)							
Expertise N (%)			**Country of origin N (%)**				
CNS	**Urological surgeon**	**Oncologist**	**Scotland**	**England**	**Wales**	**Other European countries**	**USA**
8 (17)	31 (66)	8 (17)	25 (53)	12 (26)	1 (2)	7 (15)	2 (4)

Abbreviations: HCPs (health care professionals) CNS (cancer nurse specialist), EBRT (electron beam radiotherapy), AS (active surveillance)

Table 2: Summary of results after three rounds of Delphi survey

Outcomes	Patients N = 105			HCPs N = 47			Consensus from Delphi survey
	Not important	Important	Critical	Not important	Important	Critical	
A.CANCER SPECIFIC AND SURVIVAL OUTCOMES							
1. Death from any cause	2%	6%	92%	0%	2%	98%	In
2. Death from prostate cancer	1%	4%	95%	0%	2%	98%	In
3. Death from causes other than prostate cancer*	2%	9%	89%	0%	6%	94%	In
4. Local disease recurrence	1%	5%	94%	0%	4%	96%	In
5. Distant disease recurrence/metastases	1%	3%	96%	0%	0%	100%	In
6. Disease progression (disease getting worse)	2%	5%	93%	0%	4%	96%	In
7. Need for further treatment to augment primary treatment	2%	10%	88%	0%	19%	81%	In
8. Need for salvage therapy	3%	6%	91%	0%	13%	87%	In
Applicable to active surveillance							
9. Disease reclassification	5%	6%	89%	0%	23%	77%	In
10. Need for curative treatment	5%	9%	86%	0%	4%	96%	In
Applicable to ablative procedures (cryotherapy, HIFU)							
11. Treatment failure	4%	4%	93%	0%	11%	89%	In
12. Retreatment	4%	8%	88%	0%	19%	81%	In
Applicable to surgery							
13. Positive surgical margin	3%	5%	92%	4%	49%	47%	Equivocal
B. BOWEL FUNCTION							
14. Diarrhoea	7%	82%	11%	2%	87%	11%	Equivocal
15. Faecal incontinence	4%	19%	77%	2%	9%	89%	In
16. Faecal urgency	4%	57%	39%	2%	63%	35%	Equivocal

17. Rectal bleeding	6%	38%	56%	4%	57%	39%	Equivocal
18. Rectal itch	15%	79%	6%	15%	80%	4%	Equivocal
19. Constipation	10%	80%	9%	11%	85%	4%	Equivocal
20. Bowel frequency	13%	83%	4%	7%	85%	9%	Equivocal
21. Painful bowel movements	9%	64%	27%	2%	83%	15%	Equivocal
C. URINARY FUNCTION							
22. Urge incontinence	6%	44%	50%	0%	43%	57%	Equivocal
23. Stress incontinence	7%	60%	33%	0%	49%	51%	Equivocal
24. Weak urine stream	10%	79%	11%	7%	87%	7%	Equivocal
25. Nocturia	26%	60%	14%	7%	87%	7%	Equivocal
26. Haematuria	11%	37%	52%	9%	83%	9%	Equivocal
27. Dysuria	9%	53%	38%	2%	91%	7%	Equivocal
28. Frequency	17%	68%	14%	11%	83%	7%	Equivocal
29. Urgency	11%	67%	22%	2%	89%	9%	Equivocal
30. Need for a temporary urethral catheter	27%	34%	39%	23%	72%	4%	Equivocal
31. Catheter-related problems	10%	40%	49%	13%	79%	9%	Equivocal
D. SEXUAL FUNCTION							
32. Erectile dysfunction	10%	52%	38%	0%	68%	32%	Equivocal
33. Reduced or loss of libido	8%	66%	26%	0%	94%	6%	Equivocal
34. Frequency of intercourse	14%	72%	14%	9%	89%	2%	Equivocal
35. Ejaculatory function	18%	60%	22%	21%	79%	0%	Equivocal
36. Orgasmic function	10%	63%	27%	2%	98%	0%	Equivocal
37. Sexual function	10%	61%	29%	0%	83%	17%	Equivocal
E. OPERATION SPECIFIC AND HOSPITAL-STAY OUTCOMES							
Applicable to all treatments apart from Active surveillance							
38. Duration of the procedure	39%	57%	4%	49%	51%	0%	Equivocal

39. Pain	10%	82%	8%	0%	100%	0%	Equivocal
40. Use of pain relief medications after procedure	8%	82%	10%	9%	91%	0%	Equivocal
41. Catheter duration	13%	71%	16%	17%	83%	0%	Equivocal
42. Duration of hospital stay	34%	61%	5%	13%	87%	0%	Equivocal
43. Time to full recovery	14%	71%	15%	0%	52%	48%	Equivocal
44. Time to partial recovery	17%	76%	7%	4%	93%	2%	Equivocal
Applicable to radical prostatectomy only							
45. Blood loss	18%	56%	26%	2%	82%	16%	Equivocal
F. QUALITY OF LIFE AND EMOTIONAL WELL-BEING							
46. Anxiety	14%	78%	9%	2%	89%	9%	Equivocal
47. Depression	12%	69%	19%	2%	89%	9%	Equivocal
48. Lack of confidence	16%	73%	11%	2%	89%	9%	Equivocal
49. Feeling less masculine	27%	61%	12%	2%	91%	6%	Equivocal
50. Feeling tired or fatigued	10%	73%	17%	0%	94%	6%	Equivocal
51. Overall Quality of LIfe	11%	52%	37%	0%	40%	60%	Equivocal
52. Quality of life relating to urinary function	8%	56%	37%	0%	49%	51%	Equivocal
53. Quality of life relating to sexual function	8%	64%	28%	0%	77%	23%	Equivocal
54. Quality of life relating to bowel function	6%	48%	45%	0%	49%	51%	Equivocal
55. Quality of life impact on immediate family	6%	56%	38%	0%	79%	21%	Equivocal
G. ADVERSE EVENTS DURING AND AFTER HORMONE THERAPY							
56. Hot flushes	26%	72%	2%	4%	91%	4%	Equivocal
57. Swelling of the breast tissue (gynaecomastia)	17%	70%	13%	4%	87%	9%	Equivocal
58. Loss of libido	16%	70%	14%	2%	98%	0%	Equivocal
59. Erectile dysfunction	17%	53%	29%	2%	85%	13%	Equivocal
60. Body fat gain	7%	76%	17%	4%	91%	4%	Equivocal
61. Fatigue	3%	77%	21%	2%	81%	17%	Equivocal

H. ADVERSE EVENTS DURING AND AFTER RADIATION THERAPY							
62. Anal discomfort	8%	82%	10%	0%	96%	4%	Equivocal
63. Urethral stricture	8%	21%	71%	0%	47%	53%	Equivocal
64. Radiation proctitis	9%	52%	39%	0%	53%	47%	Equivocal
65. Acute urinary retention	12%	8%	80%	0%	45%	55%	Equivocal
66. Fatigue	7%	84%	9%	0%	81%	19%	Equivocal
67. Haematuria	15%	60%	25%	4%	77%	19%	Equivocal
I. ADVERSE EVENTS DURING AND AFTER SURGERY							
68. Acute or sub-acute bowel obstruction	10%	8%	82%	0%	29%	71%	In
69. Acute urinary retention	6%	14%	80%	0%	42%	58%	Equivocal
70. Anastomotic leak	8%	18%	74%	0%	64%	36%	Equivocal
71. Blood transfusion	11%	42%	47%	2%	64%	33%	Equivocal
72. Wound problems	8%	38%	55%	2%	89%	9%	Equivocal
73. Bowel injury	6%	13%	81%	0%	11%	89%	In
74. Nerve damage or neuropraxia	8%	20%	72%	0%	53%	47%	Equivocal
75. Perioperative deaths	7%	1%	91%	0%		100%	In
76. Prolonged indwelling catheter	6%	31%	63%	7%	80%	13%	Equivocal
77. Thromboembolic disease	8%	3%	89%	0%	11%	89%	In
78. Rectourethral fistula	8%	5%	88%	0%	4%	96%	In
79. Urethral or anastomotic stricture	6%	12%	83%	0%	24%	76%	In
Additional outcomes suggested by participants in Round 1							
80. Impact on relationship with partner	10%	45%	46%	0%	57%	43%	Equivocal
81. Bladder pain	19%	45%	36%	2%	89%	9%	Equivocal
82. Urinary tract infection	19%	46%	36%	6%	89%	4%	Equivocal
83. Induction of new cancers+	9%	5%	86%	2%	53%	45%	Equivocal
84. Side effects of hormonal therapy	6%	31%	63%	0%	46%	54%	Equivocal

Key: Green cells indicate outcomes meeting consensus ‘in’. Red cells indicate ≥70% critical

*’Death from causes other than prostate cancer’ was originally voted ‘in’, but after discussion it was felt to be structurally related to ‘death from any cause’ and ‘death from prostate cancer’ and therefore voted out.

+‘Induction of new cancers’ was originally voted ‘in’ but after discussion it was felt to be too rare and late occurring an outcome to be feasibly collected in a trial setting and therefore voted out.

Table 3: Expertise and experience of consensus meeting participants

Name	Role	Expertise/Experience	Date of treatment start	City, country
Gary Akehurst	Patient	Received treatment for localised prostate cancer	November 2011	England (UK)
Robert Almquist	Patient	Received treatment for localised prostate cancer	November 2013	England (UK)
Karl Beck	Patient	Received treatment for localised prostate cancer	January 2008	Scotland (UK)
David Budd	Patient	Received treatment for localised prostate cancer	June 2013	Scotland (UK)
Alexander Ewen	Patient	Received treatment for localised prostate cancer	November 2013	Scotland (UK)
David Hurst	Patient	Received treatment for localised prostate cancer	September 2011	England (UK)
Andrew Mackie	Patient	Received treatment for localised prostate cancer	June 2012	Scotland (UK)
Hans Schreuder	Patient	Received treatment for localised prostate cancer	October 2012	England (UK)
Hashim Ahmed	HCP (Surgeon)	HIFU	NA	London, England (UK)
James N'Dow	HCP (Surgeon)/ European Association of Urology Guidelines Office	Surgery and active surveillance/ Chair of EAU Guidelines Office	NA	Aberdeen, Scotland (UK)
Judith Grant	HCP (Clinical Oncologist)	EBRT and active surveillance	NA	Aberdeen, Scotland (UK)
Justine Royle	HCP (Surgeon)	Robotic/laparoscopic radical prostatectomy	NA	Aberdeen, Scotland (UK)

Kevin Wardlaw	HCP (CNS)	Prostate cancer management	NA	Aberdeen, Scotland (UK)
Nicolas Mottet	HCP (Surgeon)/European Association of Urology Prostate cancer guideline panel	Laparoscopic radical prostatectomy/Chair of EAU Prostate cancer guideline panel	NA	St. Etienne, France
Philip Cornford	HCP (Surgeon)/European Association of Urology Prostate cancer guideline panel	Robotic radical prostatectomy/Co-chair of EAU Prostate cancer guideline panel	NA	Liverpool, England (UK)
Philip Dahm	HCP (Surgeon)/Cochrane Urology editorial group	Open radical prostatectomy/Coordinating Editor of Cochrane Urology	NA	Minneapolis, USA
Rakesh Heer	HCP (Surgeon)	Robotic radical prostatectomy	NA	Newcastle, England (UK)
Rob Jones	HCP (Medical Oncologist)/Cancer Research UK Clinical Trials Unit	Active surveillance, Director of CRUK CTU, Beatson Institute	NA	Glasgow, Scotland (UK)
Sam McClinton	HCP (Surgeon)	Surgery and active surveillance	NA	Aberdeen, Scotland (UK)
Thomas Lam	HCP (Surgeon)	Robotic/laparoscopic radical prostatectomy	NA	Aberdeen, Scotland (UK)
William Cross	HCP (Surgeon)	Robotic radical prostatectomy	NA	Leeds, England (UK)
Marion Campbell	Methodologist (Non-voting)/Health Services Research Unit	Evidence synthesis and trials/Chair of Health Services Research Unit, Aberdeen	NA	Aberdeen, Scotland (UK)
Paula Williamson	**Chair** Methodologist (Non-	Evidence synthesis, trials and COS/Chair of COMET Initiative Management Group	NA	Liverpool, England (UK)

	voting)/COMET			
Steven MacLennan	Methodologist (Non-voting)	Evidence Synthesis and qualitative research	NA	Aberdeen, Scotland (UK)
Linda Pennet	PPI/CNS (Non-voting)	Prostate cancer management	NA	Aberdeen, Scotland (UK)
Grigoris Athanasiadis	Observer	Robotic radical prostatectomy	NA	Aberdeen, Scotland (UK)
Rebecca Fish	Observer	Colorectal surgeon and PhD student developing COS in anal cancer	NA	Bristol, England (UK)

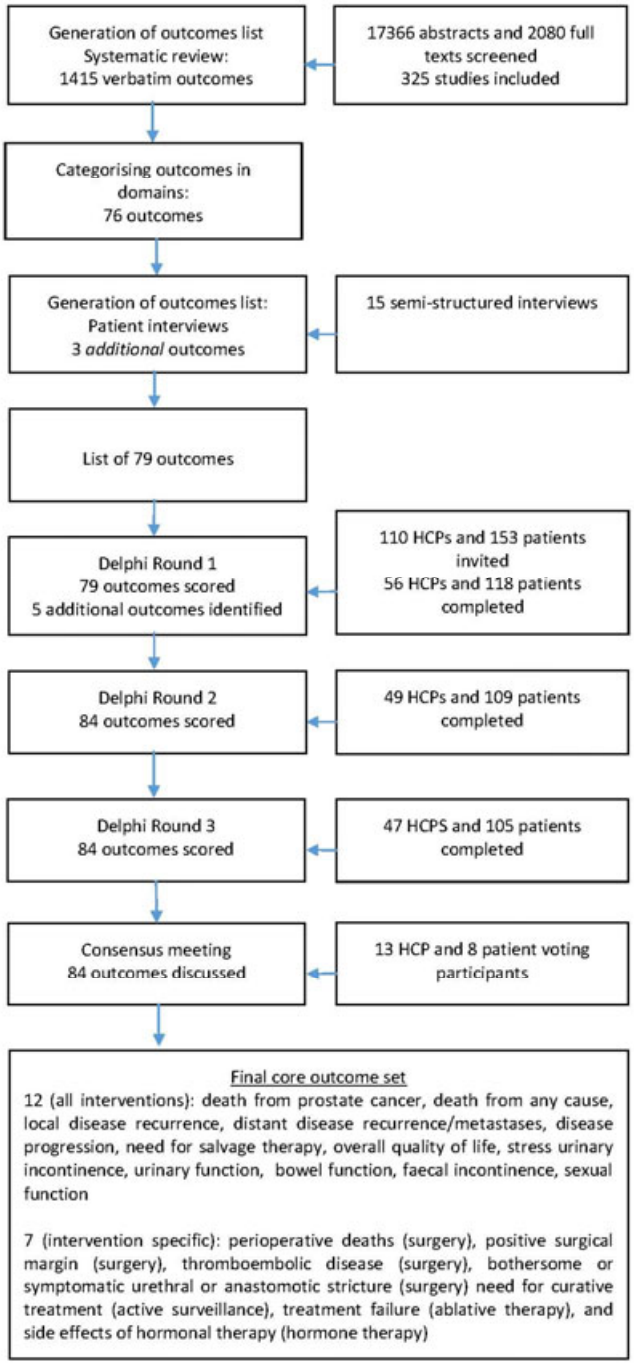
Abbreviations: HIFU (high intensity focussed ultrasound), EBRT (electron beam radiotherapy), COS (core outcome set), HCP (healthcare professional), UCAN (urological cancer charity), PCASO (prostate cancer support organisation), LPC (localised prostate cancer), PPI (patient and public involvement)

Table 4: Final Core Outcome Set for trials of interventions for localised prostate cancer

Domain	Outcome
Universal (i.e. applicable to all interventions)	
Cancer/survival	Death from prostate cancer
Cancer/survival	Death from any cause
Cancer/survival	Local disease recurrence
Cancer/survival	Distant disease recurrence/metastases
Cancer/survival	Disease progression
Cancer/survival	Need for salvage therapy
Bowel function	Faecal incontinence
Bowel function	Bowel function (including diarrhoea, faecal urgency, rectal bleeding, rectal itch, constipation, bowel frequency, and painful bowel movements)
Urinary function	Stress incontinence
Urinary function	Urinary function (including urge incontinence, weak urine stream, nocturia, haematuria, dysuria, frequency, urgency, need for temporary catheter, and catheter related problems)
Sexual function	Sexual function (including erectile dysfunction, reduced or loss of libido, frequency of intercourse, ejaculatory function, orgasmic function, and sexual function,)
Quality of life	Overall quality of life (including anxiety, depression, lack of confidence, feeling less masculine, feeling tired or fatigued, overall quality of life, quality of life relating to urinary function, quality of life relating to sexual function, quality of life relating to bowel function and quality of life impact on immediate family)
Surgery (i.e. radical prostatectomy)	
Cancer/Survival	Positive surgical margin
Adverse events	Perioperative deaths
Adverse events	Thromboembolic disease
Adverse events	Bothersome or symptomatic urethral or anastomotic stricture
Ablative therapy	

Cancer/survival	Treatment failure
Active surveillance	
Cancer/survival	Need for curative treatment
Hormone Therapy	
Adverse events	Side effects of hormonal therapy

Figure 1: Overview of core outcome set development



Appendix 1. Round one questionnaire including list of outcomes to score and definitions

Please score the following outcomes. On each page you will see a list of outcomes organised under heading such as 'adverse events' or 'bowel function 'and you will be asked to score them on a scale of 1-9, with 1 being not important at all and 9 being critically important. We have split some of the adverse events (also known as 'side-effects') up by the type of treatments that people might have because the adverse events are not exactly the same for each treatment type. Some me might have had only surgery or radiotherapy as part of their treatment, where as some men might have had both, and other men may have had hormone treatment too. Even if you didn't have a particular treatment, you might still like to score these outcomes because they might have been important in making decisions about which treatment to have. If you feel you can't answer, just click 'unable to score'. Please specify any other important outcomes, in the space provided in the last row under 'Other' and remember to score any new outcomes you suggest.

A. Cancer-specific outcomes and survival outcomes

		Not important			Important			Critical			
Outcome	**Lay description**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
Applicable to all treatments											
1. Death from any cause	This outcome refers to the death of someone from any cause, including prostate cancer.										
2. Death from prostate cancer	This outcomes refers to the death of someone as a result of prostate cancer										
3. Death from causes other than prostate cancer	This outcome refers to the death of someone from any causes other than prostate cancer.										
4. Local disease recurrence	This outcome indicates that the disease has come back locally either within the prostate, or in the surrounding area (i.e. prostate bed), following a previous cure. This includes a range of different measures, including radiological imaging combined with biopsies, the use of PSA as an indicator, positive repeat biopsies 1 year after ablative therapy (e.g. cryotherapy, HIFU, etc.), positive repeat biopsies after curative radiotherapy, etc.										
5. Distant disease recurrence/metastases	This outcome refers to someone whose cancer has spread to other parts of their body (e.g. bones, lymph nodes, etc.).										
6. Disease progression (disease getting worse)	This outcome refers to the progression of someone's cancer and is based on a combination of factors including PSA changes and/or clinical indicators of progression (i.e. disease getting worse) such as radiological imaging combined with biopsies, etc.										
7. Need for further treatment to augment primary treatment	This outcome refers to the need for a person to have additional treatment following a curative treatment. Examples include use of radiotherapy following surgery, hormonal therapy after radiotherapy, hormonal therapy after ablative therapy (e.g. HIFU, cryotherapy), etc.										
8. Need for salvage therapy	This outcome refers to the need for a person to have additional curative treatment for disease which has come back (i.e. recurred), following a previous cure.										
Applicable to active surveillance											
9. Disease reclassification	This refers to the upgrading of a person's cancer on repeat prostate biopsies (i.e. indicating that the disease has become more aggressive), or repeat radiological imaging (usually based on MRI scan) has shown more extensive or more aggressive disease. This usually triggers the need for curative treatment on patients managed initially by active surveillance.										
10. Need for curative treatment	This refers to people who have needed curative treatment during the period of active surveillance.										
Applicable to ablative procedures (cryotherapy, HIFU)											
11. Treatment failure	This outcome refers to the presence of cancer after one or more treatments, confirmed by radiological imaging (i.e. persistent disease, usually detected using MRI) or biopsy, or both. This can be performed at different time points following treatment. At some time points, this outcome can lead to repeat treatment of the same procedure (i.e. re-treatment); at longer time points (e.g. more than 1 year), it is regarded as failure of treatment, and leads to the need for a different curative treatment (i.e. salvage treatment).										
12. Retreatment	This outcome refers to the need for a person to have repeat treatment of the same procedure, usually because of persistence of disease either on repeat biopsy or radiological imaging.										
Applicable to surgery											
13. Positive surgical margin	This outcome indicates that the pathological assessment of the prostate gland after surgical removal (i.e. radical prostatectomy) has shown cancer at the edges of the prostate specimen. This implies that there may be some cancer left behind, although this is unproven, and its actual impact on long-term outcomes (e.g. survival) is uncertain.										
Other (please specify)											

B. Bowel Function

		Not important			Important			Critical			
Outcome	**Lay description**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
14. Diarrhoea	Watery stools										
15. Faecal incontinence	Uncontrolled leakage of stools										
16. Faecal urgency	Having to rush to get to the toilet to open bowels										
17. Rectal bleeding	Bleeding from the back passage										

18. Rectal itch	Itching inside the back passage										
19. Constipation	Difficulty in opening bowels										
20. Bowel frequency	Having to go to the toilet more frequently than previously										
21. Painful bowel movements	Pain in the back passage during defecation.										
Other (please specify)											

C. Urinary Function

		Not important					Important		Critical		
Outcome	**Lay description**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
22. Urge incontinence	Uncontrolled leakage of urine associated with a sensation of having to rush to get to a toilet to urinate										
23. Stress incontinence	Uncontrolled leakage of urine associated with coughing, sneezing, running, exercising, etc.										
24. Weak urine stream	Having a very poor or intermittent urinary stream										
25. Nocturia	Having to get up during the night to urinate										
26. Haematuria	Visible blood in the urine										
27. Dysuria	Pain when urinating										
28. Frequency	Needing to pass urine more frequently										
29. Urgency	Feeling the sensation for having to rush to get to a toilet to urinate										
30. Need for a temporary urethral catheter	Most patients who have surgery for prostate cancer receive a urethral catheter temporarily ranging from a day to 2 weeks depending on the nature of the surgical treatment. This question relates to the need for a catheter as part of the surgical procedure.										
31. Catheter-related problems	These refer to problems such as catheter blocking off, leaking, bladder spasms, discomfort during catheter removal, etc.										
Other (please specify)											

D. Sexual Function

		Not important					Important		Critical		
Outcome	**Lay description**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
32. Erectile dysfunction	Inability to have erections sufficient for penetrative intercourse, or the quality of erections being poorer										

	following treatment.										
33. Reduced or loss of libido	Reduced or loss of interest in having sex										
34. Frequency of intercourse	Amount of times being able to have sex										
35. Ejaculatory function	Problems with ejaculation following treatment (e.g. unable to ejaculate, painful, blood in semen, dry ejaculate, reduced semen amount, etc.)										
36. Orgasmic function	Problems with achieving orgasm or climax during sex.										
37. Sexual function	General term referring to combination of functions, including libido, erectile function, ejaculatory function and orgasmic function.										
Other (please specify)											

E. Operation-specific and hospital-stay outcomes

		Not important					Important		Critical		
Outcome	**Lay description**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
Applicable to all treatments apart from active surveillance											
38. Duration of the procedure	This outcome is relevant to a person who has had surgery (including radical prostatectomy, cryotherapy or HIFU) only. It refers to how long it takes to complete the procedure.										
39. Pain	This outcome is relevant to people who have had any interventions. It refers to pain experienced during and immediately after the intervention.										
40. Use of pain relief medications after procedure	This outcome refers to the amount of medication for pain relief patients need after their intervention										
41. Catheter duration	This outcome refers to the length of time a urethral catheter is left in after a procedure										
42. Duration of hospital stay	This outcome is only relevant to an individual who has a procedure requiring them to stay in hospital. It refers to the length of time spent in hospital during and after the treatment.										
43. Time to full recovery	This refers to the length of time it takes for a person to return to their normal level of activities and functioning (i.e. day-to-day life) after their intervention is completed. This includes things like being able to drive, going to work, and being involved in leisure activities and hobbies (e.g. playing golf, walking, gardening, etc.).										
44. Time to partial recovery	This refers to the length of time it takes for a person to achieve a partial return to their normal level of activities and functioning (i.e. day-to-day life) after their intervention is completed. For example, being able to walk only with assistance, being able to drink fluids but not tolerate solid diet, being able to walk but not climb stairs, etc.										

Applicable to radical prostatectomy only											
45. Blood loss	This outcome is relevant to a person who has had radical prostatectomy only. It refers to the volume of blood lost during a surgical intervention for prostate cancer.										
Other (please specify)											

F. Quality of life and Emotional well-being

		Not important			Important			Critical			
Outcome	**Lay description**	1	2	3	4	5	6	7	8	9	**Unable to score**
46. Anxiety	Feeling anxious either during or after treatment.										
47. Depression	Feeling depressed either during or after treatment.										
48. Lack of confidence	Feeling less confident about life in general (e.g. in going out, socialising, etc.).										
49. Feeling less masculine	Feeling less masculine as a result of treatment.										
50. Feeling tired or fatigued	Feeling tired, fatigued or lethargic either during or after treatment.										
51. Overall quality of life	Quality of life in general related to physical and emotional wellbeing.										
52. Quality of life relating to urinary function	Quality of life specifically related to urinary function.										
53. Quality of life relating to sexual function	Quality of life specifically related to sexual function.										
54. Quality of life relating to bowel function	Quality of life specifically related to bowel function.										
55. Quality of life impact on immediate family	Impact of treatment on immediate family members in terms of their quality of life.										
Other (please specify)											

G. Adverse events (unwanted side effects) during and after Hormone Therapy

		Not important			Important			Critical			
Outcome	**Lay description**	1	2	3	4	5	6	7	8	9	**Unable to score**
56. Hot flushes	Sudden feeling of warmness, usually experienced most intensely over the face, neck and chest, and may be associated with redness over the skin and sweating.										
57. Swelling of the breast tissue (gynaecomastia)	Generalised swelling or enlargement of the breasts due to hormonal changes.										
58. Loss of libido	Loss of interest in, and desire for, sexual activity.										
59. Erectile dysfunction	Inability to have erections sufficient for penetrative intercourse, or the quality of erections being poorer following treatment.										
60. Body fat gain	General body fat gain										
61. Fatigue	Extreme tiredness or lethargy.										
Other (please specify)											

H. Adverse events (unwanted side effects) during and after radiation therapy (including External Beam Radiotherapy and Brachytherapy)

		Not important			Important			Critical			
Outcome	**Lay description**	1	2	3	4	5	6	7	8	9	**Unable to score**
62. Anal discomfort	Discomfort in the back passage.										
63. Urethral stricture	Blockage to the water passage within the penis due to formation of scar tissue.										
64. Radiation proctitis	Inflammation of the rectum caused by radiotherapy										
65. Acute urinary retention	Inability to pass water, sometimes resulting in painful swelling of the bladder.										
66. Fatigue	Feeling tired or lethargic.										
67. Haematuria	Passing blood mixed with urine.										
Other (please specify)											

I. Adverse events for surgery (including open, laparoscopic and robotic surgery, cryotherapy and HIFU

		Not important			Important			Critical			
Outcome	**Lay description**	1	2	3	4	5	6	7	8	9	**Unable to score**
68. Acute or sub-acute bowel obstruction	Sudden blockage to the gut due to formation of scar tissue within the gut or surrounding areas.										
69. Acute urinary retention	Inability to pass water resulting in painful swelling of the bladder.										
70. Anastomotic leak	Leakage of urine as a result of the joint between the bladder and water pipe not being watertight.										

71. Blood transfusion	Need for blood being replaced due to excessive blood loss.									
72. Wound problems	Opening of abdominal or pelvic wound due to the wound breaking down, or wound infection.									
73. Bowel injury	Accidental damage to the gut.									
74. Nerve damage or neuropraxia	Accidental damage or pressure on the obturator nerve during surgery which causes temporary weakness of the legs.									
75. Perioperative deaths	Death occurring either during surgery or in the first week following surgery.									
76. Prolonged indwelling catheter	Prolonged need for a urethral catheter following surgery.									
77. Thromboembolic disease	Blood clot in the blood vessels draining blood from the legs (DVT), or vessels supplying blood to the lungs (pulmonary embolism).									
78. Rectourethral fistula	Development of an abnormal channel which creates a connection between the rectum and water pipe, usually due to damage to the rectum occurring during surgery.									
79. Urethral or anastomotic stricture	Narrowing of the water pipe or bladder neck area due to scar tissue causing blockage.									
Other (please specify)										

Appendix 2: Detailed Characteristics of HCPs completing all 3 Delphi survey rounds

Name	**City, country of residence**	**Expertise**
Alan Mcneill	Edinburgh, Scotland (UK)	Surgery (lap)
Alasdair Innes	Edinburgh, Scotland (UK)	Urology CNS
Alessandro Volpe	Novara, Italy	Surgery (robotic)
Axel Bex	Amsterdam, The Netherlands	Surgery (robotic)
Axel Merseburger	Hannover, Germany	Surgery
Balazs Binnyei	Aberdeen, Scotland (UK)	Oncology (medical)
Borje Ljungberg	Umea, Sweden	Surgery
Brian Corr	Inverness, Scotland (UK)	Urology CNS
Danny Lynch	Aberdeen, Scotland (UK)	Oncology CNS
David Douglas	Inverness, Scotland (UK)	Surgery (lap/robotic)

Debbie Munro	Aberdeen, Scotland (UK)	Urology CNS
Duncan McLaren	Newcastle, England (UK)	Oncology (clinical)
Eric Borg	Aberdeen, Scotland (UK)	Urology CNS
Graham Macdonald	Aberdeen, Scotland (UK)	Oncology (clinical)
Grant Stewart	Edinburgh, Scotland (UK)	Surgery (lap)
Hashim Ahmed	London, England (UK)	Surgery (HIFU)
Henk Van der Poel	Amsterdam, The Netherlands	Surgery (robotic)
Hugh Mostafid	Basingstoke, England (UK)	Surgery (lap)
Ian Pearce	Manchester, England (UK)	Surgery (lap)
James N'Dow	Aberdeen, Scotland (UK)	Surgery
Jim Catto	Sheffield, England (UK)	Surgery (robotic)
Judith Grant	Aberdeen, Scotland (UK)	Oncology (clinical)
Justine Royle	Aberdeen, Scotland (UK)	Surgery (lap/robotic)
Kevin Wardlaw	Aberdeen, Scotland (UK)	Urology CNS
Lesley Simpson	Aberdeen, Scotland (UK)	Urology CNS
Linda Pennet	Aberdeen, Scotland (UK)	Urology CNS
Malcolm Mason	Cardiff, Wales (UK)	Oncology (clinical)
Nicholas Cohen	Aberdeen, Scotland (UK)	Surgery
Nicolas Mottet	St. Etienne, France	Surgery (lap)
Pam Barker	Aberdeen, Scotland (UK)	Surgery
Paul Abel	London, England (UK)	Surgery
Paul Halliday	Dundee, Scotland (UK)	Surgery
Peter Cooke	Wolverhampton, England (UK)	Surgery
Philip Cornford	Liverpool, England (UK)	Surgery (robotic)
Philipp Dahm	Minneapolis, USA	Surgery

Robert Jones	Glasgow, Scotland (UK)	Oncology (medical)
Robert Mills	Norwich, England (UK)	Surgery
Roger Kocklebergh	Leicester, England (UK)	Surgery
Sam McClinton	Aberdeen, Scotland (UK)	Surgery
Satchi Swami	Aberdeen, Scotland (UK)	Surgery
Steve Leung	Dunfermline, Scotland (UK)	Surgery
Steven Canfield	Houston, USA	Surgery (robotic)
Thomas Lam	Aberdeen, Scotland (UK)	Surgery (lap/robotic)
Thomas Wiegel	Ulm, Germany	Oncology (clinical)
William Cross	Leeds, England (UK)	Surgery (robotic)

Appendix 3: Results of voting for all outcomes voted on during consensus group meeting

Outcome (applicable interventions)	Not important	Important	Critical
A.CANCER SPECIFIC AND SURVIVAL OUTCOMES			
1. Death from any cause (universal)	5%	0%	95%
2. Death from prostate cancer (universal)	0%	5%	95%
3. Death from causes other than prostate cancer (universal) ++	5%	0%	95%
4. Local disease recurrence (universal)	0%	19%	81%
5. Distant disease recurrence/metastases (universal)	0%	5%	95%
6. Disease progression (universal)	0%	5%	95%
7. Need for further treatment to augment primary treatment (universal)	14%	57%	29%
8. Need for salvage therapy (universal)	0%	10%	91%
9. Disease reclassification (Active surveillance)	0%	33%	67%
10. Need for curative treatment (Active surveillance)	0%	14%	86%
11. Treatment failure (Ablative)	0%	5%	95%
12. Retreatment (Ablative)	10%	29%	62%
13. Positive surgical margin (Surgery)	0%	24%	76%
B. BOWEL FUNCTION			
14. Bowel function (universal)*	0%	20%	80%
15. Faecal incontinence (universal)	0%	14%	86%
C. URINARY FUNCTION			
23. Stress incontinence (universal)	14%	14%	71%
24. Urinary Function (universal)*	0%	5%	95%
26. Haematuria (universal)	15%	70%	15%
30. Need for temporary catheter (universal)	40%	60%	0%
31. Catheter-related problems (urinary function)	30%	60%	10%
D. SEXUAL FUNCTION			
37. Sexual Function (universal)*	0%	10%	85%
E. OPERATION SPECIFIC AND HOSPITAL-STAY OUTCOMES			
Applicable to all treatments apart from Active surveillance			
43. Time to full recovery (universal)	14%	67%	19%
F. QUALITY OF LIFE AND EMOTIONAL WELL-BEING			
51. Overall Quality of Life (universal)	5%	10%	86%
52. Quality of life relating to urinary function (universal)	100%	0%	0%
54. Quality of life relating to bowel function (universal)	95%	5%	0%
H. ADVERSE EVENTS DURING AND AFTER RADIATION THERAPY			
63. Bothersome or symptomatic Urethral stricture	0%	24%	76%

65. Acute urinary retention (all interventions)	10%	48%	43%
66. Fatigue (all interventions) (REWORDED)	0%	35%	65%
68. Acute or sub-acute bowel obstruction (AE surgery)	0%	38%	62%
69. Acute urinary retentionall treatments	100%	0%	0%
I. ADVERSE EVENTS DURING AND AFTER SURGERY			
70. Anastomotic leak	5%	76%	19%
72. Wound problems	29%	62%	10%
74. Nerve damage or neuropraxia	38%	24%	0%
75. Perioperative deaths	5%	5%	91%
77. Thromboembolic disease	0%	29%	71%
79. Bothersome or symptomatic urethral or anastomotic stricture	0%	33%	67%
Additional outcomes suggested by participants in Round 1 of Delphi			
80. Impact on relationship with partner	0%	80%	20%
83. Induction of new cancers §	10%	24%	76%
84. Side effects of hormonal therapy	0%	5%	95%
85. 'Bowel injury' and 'rectourethral fistula' considered together*	5%	47%	47%

Key: Green cells indicate outcomes meeting consensus 'in'. Red cells indicate ≥70% critical

++ Although initially voted 'in', 'death from causes other than prostate cancer' was subsequently discussed and voted out because it is structurally related to 'death from any cause' and 'death from prostate cancer'.

§ Although initially voted 'in', 'Induction of new cancers' was subsequently discussed and voted out because it was considered to be very rare and late occurring and therefore unlikely to be feasible to collect in effectiveness trials.

*Outcomes re-categorised during consensus meeting

'Bowel function' includes: diarrhoea, faecal urgency, rectal bleeding, rectal itch, constipation, bowel frequency, and painful bowel movements

'Urinary function' includes: urge incontinence, weak urine stream, nocturia, haematuria, dysuria, frequency, urgency, need for temporary catheter, and catheter related problems

'Sexual function' includes: erectile dysfunction, reduced or loss of libido, frequency of intercourse, ejaculatory function, orgasmic function, and sexual function

'Overall quality of life' includes: anxiety, depression, lack of confidence, feeling less masculine, feeling tired or fatigued, overall quality of life, quality of life relating to urinary function, quality of life relating to sexual function, quality of life relating to bowel function and quality of life impact on immediate family