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European Association of Urology

Prostate Cancer

Updating and Integrating Core Outcome Sets for Localised, Locally Advanced, Metastatic, and Nonmetastatic Castration-resistant Prostate Cancer: An Update from the PIONEER Consortium

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Article info

Article history:
Accepted January 20, 2022

Associate Editor:
James Catto

Abstract

Context: Harmonisation of outcome reporting and definitions for clinical trials and routine patient records can enable health care systems to provide more efficient outcome-driven and patient-centred interventions. We report on the work of the PIONEER Consortium in this context for prostate cancer (PCa).

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https://doi.org/10.1016/j.eururo.2022.01.042

Keywords:
Prostate cancer
Patient pathway
Comparative effectiveness research
Core outcome sets
Standardised outcome sets
Effectiveness trials
Outcomes
Randomised controlled trials
Systematic reviews
Big data
Real-world data

Objective: To update and integrate existing core outcome sets (COS) for PCa for the different stages of the disease, assess their applicability, and develop standardised definitions of prioritised outcomes.
Evidence acquisition: We followed a four-stage process involving: (1) systematic reviews; (2) qualitative interviews; (3) expert group meetings to agree standardised terminologies; and (4) recommendations for the most appropriate definitions of clinician-reported outcomes.
Evidence synthesis: Following four systematic reviews, a multinational interview study, and expert group consensus meetings, we defined the most clinically suitable definitions for (1) COS for localised and locally advanced PCa and (2) COS for metastatic and nonmetastatic castration-resistant PCa. No new outcomes were identified in our COS for localised and locally advanced PCa. For our COS for metastatic and nonmetastatic castration-resistant PCa, nine new core outcomes were identified.
Conclusions: These are the first COS for PCa for which the definitions of prioritised outcomes have been surveyed in a systematic, transparent, and replicable way. This is also the first time that outcome definitions across all prostate cancer COS have been agreed on by a multidisciplinary expert group and recommended for use in research and clinical practice. To limit heterogeneity across research, these COS should be recommended for future effectiveness trials, systematic reviews, guidelines and clinical practice of localised and metastatic PCa.
Patient summary: Patient outcomes after treatment for prostate cancer (PCa) are difficult to compare because of variability. To allow better use of data from patients with PCa, the PIONEER Consortium has standardised and recommended outcomes (and their definitions) that should be collected as a minimum in all future studies.

1. Introduction

Prostate cancer (PCa) accounts for 15% of all cancers diagnosed [1]. The associated burden on health care systems is €8.4 billion per year in the EU [2]. However, current PCa intervention effectiveness trials are not as helpful as they could be owing to a lack of standardisation of outcome definitions and measurements [3–5]. This compromises the impact and clinical applicability of the evidence base in systematic reviews, health technology assessments, and clinical practice guidelines [5–9].

Core outcome sets (COS), an agreed minimum set of outcomes that should be measured and reported in all clinical trials, can mitigate against selective outcome reporting, address heterogeneity in outcome definitions and measurements, and facilitate evidence synthesis [10]. Two COS for localised PCa already exist. One, the Core Outcome Measures for Prostate Cancer Effectiveness Trials (COMPACTERS) [11], was developed for clinical effectiveness trials using the methods advocated by the Core Outcome Measures in Effectiveness Trials (COMET) initiative [10]. The other is a "standard set" produced by the International Consortium for Health Outcome Measurement (ICHOM) group for use in clinical audits [12]. The outcomes included in both sets overlap conceptually, but the terminology differs. The ICHOM standard outcome sets were developed specifically for clinical audits, while the COMPACTERS COS for localised PCa was developed for effectiveness randomised controlled trials (RCTs), and both were published more than 5 yr ago.

Our aim was to update the systematic reviews and combine these two existing COS for conceptual clarity and to promote a unified COS for use in clinical audits, RCTs, systematic reviews, guidelines, and real-world evidence projects. For metastatic PCa, an ICHOM standard set also already exists [13], but no qualitative research was conducted to fully understand the patient perspective during the process. We therefore aimed to address this research gap as well.

The existing COS for PCa were updated in a process led by the PIONEER Consortium (Prostate Cancer Diagnosis and Treatment Enhancement Through the Power of Big Data in Europe), an international collaboration led by the European Association of Urology (EAU) that aims to use big-data technologies to improve guideline development and clinical practice [14].

2. Evidence acquisition

We report our overall study in accordance with the Core Outcome Set-Standards for Reporting (COS-STAR) statement (Supplementary Table 1) [15], whereas the qualitative aspects of the study are reported according to the Consolidated Criteria for Reporting Qualitative Studies (COREQ; Supplementary Table 2) [16].

We followed a four-stage process to develop a PIONEER COS for PCa (Fig. 1) that involved: (1) systematic reviews of effectiveness trials to identify currently reported outcomes; (2) expert group meetings to agree standardised terminology; (3) qualitative interviews to understand patient perspectives on important outcomes; and (4) recommendations for the most appropriate definitions of clinician-reported outcomes (ClinROs). Our recommendations on patient-reported outcome measures (PROMs) with the best measurement properties that are most feasible for use in research and clinical practice are reported in a related

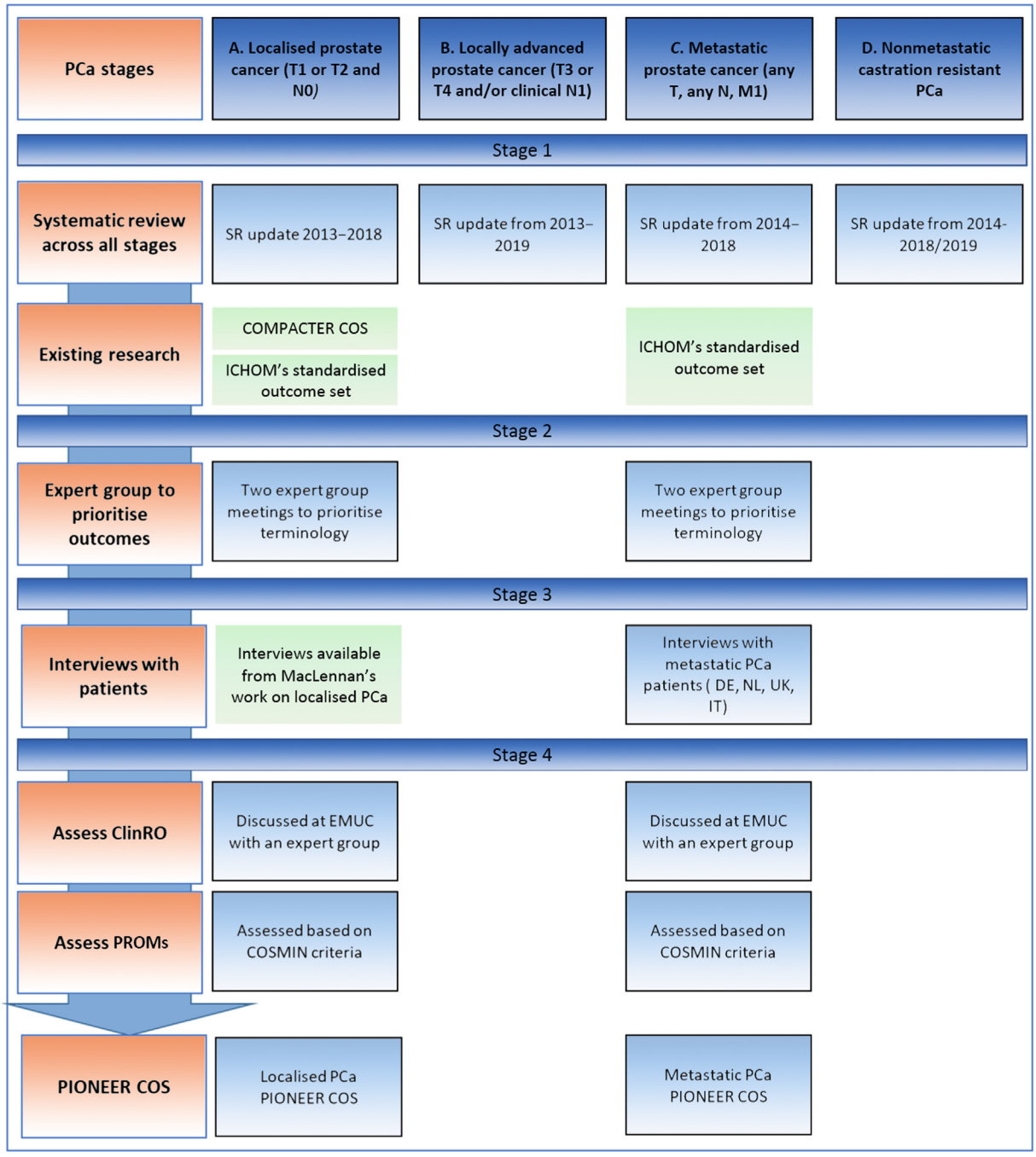

Fig. 1 – Overview of the research undertaken to develop the PIONEER core outcome set (COS). ClinRO = clinician-reported outcome; DE = Denmark; EMUC = European Multidisciplinary Congress on Urological Cancers; IT = Italy; NL = Netherlands; PCa = prostate cancer; PROMs = patient-reported outcome measures; SR = systematic review.

manuscript [17]. ClinROs and PROMs are complementary and should be implemented in tandem.

Our original aim was to develop separate COS for (1) localised PCa, (2) locally advanced PCa, (3) metastatic PCa (including both castration-resistant and hormone-sensitive metastatic PCa), and (d) nonmetastatic castration-resistant PCa (nmCRPC). The interventions within the scope for each disease stage are shown in Fig. 1. However, to avoid duplication of effort and potential replication, we decided to first assess whether the existing COS for localised PCa are also applicable to locally advanced PCa, and whether the existing COS for metastatic PCa are applicable to nmCRPC. The clinical content experts reviewed the outcomes in the existing COS and proposed that even though there were important prognosis differences between these clinical groups, for the purposes of COS creation it was justifiable to combine these groups given that many of the treatments are similar. The patient advocates attending the consensus meetings (representing the European Cancer Patient Coalition, Europa Uomo, and Selbsthilfe Prostatakrebs) also agreed this was reasonable under these circumstances. Furthermore, as the main results tables show, many of the core

outcomes are common across the whole disease spectrum, although the definitions and measurements vary. Therefore, we decided to suspend the requirement for a separate COS for locally advanced PCa and to recommend use of the COS for localised PCa for this population in the meantime. Likewise, the COS for metastatic PCa should be used for the nmCRPC population. Nevertheless, the results of the systematic reviews addressing the outcomes used for locally advanced PCa and nmCRPC are described below.

We did not publish our protocol, but our methods are informed by those outlined in the COMET handbook [10], Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) handbook [18] and based on our earlier protocols for the COS for localised PCa [19]. We outline our methodological approach here in brief, and more detail is provided in the Supplementary material.

2.1. Stage 1: systematic review

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20] for the four systematic reviews. The scope of each systematic review is clarified in the Supplementary material.

2.1.1. Search strategy

We searched for systematic reviews on intervention effectiveness. Systematic reviews and the RCTs they included published in English between January 2013 and March 2021 for localised and locally advanced PCa, and between January 2014 and March 2021 for metastatic PCa (CRPC and hormone-sensitive PCa) and nmCRPC were included. The search strategy is shown in Supplementary Table 3. The search cutoff dates were chosen to reflect the last updates of these reviews by the COMPACTERS and ICHOM groups [10,11]. The aims of our systematic review was (1) to check whether any new RCT outcomes had been identified in the interim period; (2) to identify any outcomes that were unique to the locally advanced PCa or nmCRPC setting; and (3) to identify outcome definitions. Two researchers (L.M. and M.L.) screened the literature identified. We also manually searched the reference sections of the latest EAU PCa guidelines for additional systematic reviews and RCTs.

2.1.2. Data synthesis

We compared the outcomes reported in the studies included in our review with the outcomes identified in both the ICHOM standard set [12] and the original COMPACTERS [11] systematic review (ie, before the outcomes were prioritised in the final COS). The COMPACTERS COS [12] and the ICHOM standard set [11] largely overlap for the localised PCa setting, but they use different terms to describe similar clinical constructs. Therefore, we used the outcome taxonomy developed by Dodd et al [21] as a structure to organise the outcomes.

Two independent researchers (L.M. and M.L.) compared the outcomes identified in studies of locally advanced PCa to the COMPACTERS COS [11] and ICHOM standard set [12] for localised PCa, and the nmCRPC outcomes to the ICHOM standard set for metastatic PCa [13] to identify potential overlap. In cases of disagreement, a third reviewer arbitrated (M.V.H. or A.B.). As clarified above, clinical experts decided in consultation with our research team to develop only two PIONEER COS, one covering localised and locally advanced PCa and the other covering metastatic PCa and nmCRPC.

2.2. Stage 2: consensus meetings

To homogenise the terminology used for each outcome for both the COS for localised/locally advanced PCa and the COS for metastatic PCa/nmCRPC, we held two consecutive consensus meetings with a multidisciplinary stakeholder group. The participants for the consensus meeting were purposively sampled for expertise in PCa management and research, representing key stakeholder groups: patients, urologists, radiation oncologists, medical oncologists, nurses, and pathologists (Supplementary Table 3). Further methodological details are provided in the Supplementary material.

2.3. Stage 3: qualitative interviews

The qualitative interviews were carried out as a cross-sectional exploration of what outcomes men who have been treated for advanced/metastatic PCa in Europe regard as important. This work had already been conducted for localised PCa as part of COMPACTERS [11,19]. More methodological details are provided in the Supplementary material.

2.4. Stage 4: definition of ClinROs

Using the definitions identified in the systematic reviews and organised within the common terminology, we created summary cards to list the various definitions used for each core outcome identified. Before the consensus meeting, the core research team met (Milan, October 2019) to discuss all definitions by outcome. For many definitions that were the same but worded differently, we incorporated constituent parts of the definition into a single definition but kept track of how many studies had used this definition and included this in the summary cards, along with the interventions to which the outcome was applicable. Many outcome definitions were used in only one study. Hence, to make the task more manageable for consensus meeting participants, we only included definitions that were used in at least three studies. More methodological details are provided in the Supplementary material.

During the consensus meeting, consensus was defined as 70% or more of participants choosing one definition. It was acceptable to change the terminology or subsume an outcome within another outcome if the definitions were deemed to make a core outcome obsolete, but the majority of the group (at least 70%) had to support such a decision. In addition, when different treatment types necessitated different definitions of the same outcome, this was acceptable.

3. Evidence synthesis

3.1. Stage 1: systematic review

3.1.1. Localised PCa

Searches identified 1269 citations, from which 67 systematic reviews were retained for full-text screening. Forty-

two systematic reviews met the inclusion criteria, among which 13 RCTs reported effectiveness outcomes [22–34] (Supplementary Fig. 1). No new outcomes beyond those included in COMPACTERS were identified. The outcomes cover survival, treatment toxicity, and patient functional status. We mapped all outcomes according to the 38-item Dodd taxonomy [21] (Table 1).

3.1.2. Locally advanced PCa

Searches identified 1648 citations. Fifty-six systematic reviews were suitable for full-text screening. Twelve RCTs met the inclusion criteria [22–24,35–46] (Supplementary Fig. 2). All outcomes from these RCTs were extracted. There were no new outcomes identified beyond those included in COMPACTERS (Supplementary Table 4).

3.1.3. Metastatic PCa

Literature searches identified 1249 citations. Sixty-three systematic reviews were included for full-text screening and 36 RCTs met the inclusion criteria [6–38,47–53] (Supplementary Fig. 3). Table 2 summarises the outcomes identified and equivalent outcome terms in the ICHOM standard set. We identified four new outcomes: biochemical progression-free survival, radiographic progression-free survival, clinical progression-free survival, and prostate-specific antigen (PSA) response. To encourage homogeneous data reporting, we mapped all outcomes according to the Dodd taxonomy [21].

3.1.4. Nonmetastatic CRPC

Literature searches identified 1365 citations for men with nmCRPC, metastatic CRPC, HRPC, or metastatic PC, from which five RCTs met the inclusion criteria [54–58] (Supplementary Fig. 4). Table 3 presents the additional outcomes (and their definitions) for nmCRPC that differed from the already identified outcomes for metastatic PCa, comprising time to subsequent neoplastic therapy, time to metastasis, time to symptomatic progression and second progression-free survival.

3.2. Stage 2: consensus meeting

We held two consensus meetings with a multidisciplinary expert group.

3.2.1. Localised PCa

Consensus was reached for all outcomes and changes in terminology were suggested to ensure consistency (Table 4).

3.2.2. Metastatic PCa

Consensus was reached and we decided to include all five newly identified outcomes in the final PIONEER outcome set (Table 5).

3.3. Stage 3: qualitative interviews

Interviews were conducted with 27 patients from European countries including England, Scotland, Ireland, Switzerland, the Netherlands, and Germany. Patient age ranged from 52 to 89 yr and a variety of treatments had been received (Supplementary Table 5). Outcomes mentioned by at least two participants are listed in Supplementary Table 6 along with frequency (number of patients who discussed this outcome) and a quotation to illustrate the outcome.

Patients highlighted the importance of oncological outcomes. Functional outcomes related to urinary, bowel, and sexual functions were also frequently described as important. Many adverse events were discussed as relevant, with hot flashes, pain, hair loss, skin changes, and taste changes raised most frequently. Quality of life (QoL) and life impact outcomes were often mentioned by patients (eg, vitality, fatigue, anxiety, feeling overwhelmed, and fear of progression and dying; Supplementary Table 6).

We cross-referenced outcomes identified in the interview study with those included in our COS for metastatic PCa (Tables 2 and 5). No new effectiveness outcomes regarded as important by men treated for advanced/metastatic PCa beyond those already found in the systematic reviews and captured in the ICHOM standard set for metastatic PCa were identified in the interviews. However, some of the outcomes with a life impact related to emotional functioning and wellbeing, such as fear of progression and fear of dying, may not be adequately captured.

3.4. Stage 4: definition of ClinROs

We held an expert meeting to discuss various definitions available for the ClinROs identified with a multistakeholder group (Supplementary Table 7). Tables 4 and 5 present the terminology suggested during the consensus meeting and the completed COS suggested by PIONEER.

3.4.1. Localised PCa

Table 4 presents the results of the voting. There was consensus that there is no need for definitions for the outcomes "Need for salvage therapy" and "Retreatment", since these are covered in definitions provided for other outcomes.

3.4.2. Metastatic PCa

The outcomes of the voting session after discussion are presented in Table 5.

3.5. Discussion

The goal of this extensive PIONEER work was to (1) update the existing COS for PCa for the different stages of disease from 2013 (for localised PCa) and 2014 (metastatic PCa) onwards; (2) integrate the existing COS; and (3) provide guidance for clinical integration in daily practice. This should help in improving efficient searching, reporting, and classification. In addition, we assessed the applicability of the COS and developed standardised definitions for prioritised ClinROs.

First, our work shows the persisting problem of data heterogeneity, with multiple terms used in different trials to describe the same outcome. For example, outcomes related to PSA relapse, which is key in follow-up after radical treatment, were very often reported in the RCTs identified, but with different terminology (eg, biochemical recurrence [BCR], time to BCR, BCR-free survival, PSA relapse, and biochemical failure). Through our process we were able to capture this heterogeneity and prioritise and extract the most suitable outcome term. Such umbrella

Table 1 – Organisation of outcomes within the 38-item Dodd taxonomy: original terms used in previous research and outcome terms decided on by PIONEER expert groups after two rounds of consensus meetings for the localised PCa setting

Core area(s); domain (s)	**COMPACTERS COS**	**ICHOM standard set**	**PIONEER COS for localised PCa**
Death; 1: Mortality/survival	Death from any cause	Overall survival	Overall survival
	Death from PCa	Cause-specific survival	PCa-specific survival
Physiological or clinical; 16: Outcomes relating to neoplasms	Disease progression	Biochemical recurrence	Biochemical recurrence
	Local disease recurrence		Local disease recurrence
	Distant disease recurrence/metastases	Metastasis-free survival	Distant disease recurrence/metastases
	Positive surgical margins (surgery)		Positive surgical margins (surgery)
Physiological or clinical; 16: Outcomes relating to neoplasms AND **Life impact**; 32: Delivery of care	Treatment failure (applicable to ablative procedures [cryotherapy, HIFU])		Treatment failure (applicable to ablative procedures [cryotherapy, HIFU])
Resource use; 66: Need for further intervention	Need for salvage therapy		Need for salvage therapy
	Need for curative treatment (applicable to active surveillance specifically)		Need for curative treatment (applicable to active surveillance specifically)
	Retreatment (ablative treatment)		Retreatment (applicable to ablative procedures [cryotherapy, HIFU])
Physiological or clinical; 8: Gastrointestinal outcomes	Bowel function (including diarrhoea, faecal urgency, rectal bleeding, rectal itch, constipation, bowel frequency, and painful bowel movements) Faecal incontinence	Bowel function (including urgency, frequency, incontinence, rectal bleeding, and painful bowel movements)	Bowel dysfunction (including diarrhoea, faecal urgency, rectal bleeding, rectal itch, constipation, bowel frequency, painful bowel movements, faecal incontinence)
Physiological or clinical; 19: Renal and urinary outcomes	Urinary function (including urge incontinence, weak urine stream, nocturia, haematuria, dysuria, frequency, urgency, need for temporary catheter, and catheter-related problems) Stress incontinence	Urinary function (including urinary incontinence, urinary frequency, obstruction, irritation)	Urinary dysfunction (including LUTS, urge incontinence, weak urine stream, nocturia, haematuria, dysuria, frequency, urgency, need for temporary catheter and catheter-related problems, stress incontinence)
Physiological or clinical; 20: Reproductive system and breast outcomes AND **Life impact**; 28: Emotional functioning/wellbeing AND 25: Physical functioning	Sexual function (including erectile dysfunction, reduced or loss of libido, frequency of intercourse, ejaculatory function, orgasmic function, and sexual function)	Sexual function (including erectile dysfunction, reduced or loss of libido, frequency of intercourse, sexual function, and use of medications or devices to aid or improve erections)	Sexual dysfunction (including erectile dysfunction, reduced or loss of libido, frequency of intercourse, ejaculatory function, orgasmic function, and sexual function)
Adverse events; 38: Adverse events/effects	Side effects of hormonal therapy	Hormonal symptoms scores	Side effects of hormonal therapy
Adverse events; 38: Adverse events / effects	Perioperative death (surgery-specific)	Major surgical complications	Major surgical complications including: Perioperative deaths (surgery-specific) Thromboembolic disease (surgery-specific) Bothersome or symptomatic urethral or anastomotic stricture (surgery-specific)
Adverse events; 38: Adverse events/effects AND **Physiological or clinical**; 2: Blood and lymphatic system outcomes	Thromboembolic disease (surgery-specific)		
	Bothersome or symptomatic urethral or anastomotic stricture (surgery-specific)		
Adverse events; 38: Adverse events / effects		Major radiation complications	Radiation toxicity/major radiation complication (including, for example, fatigue, bothersome or symptomatic urethral stricture, acute urinary retention, acute or subacute bowel obstruction/bowel dysfunction)

Table 1 (*continued*)

Core area(s); domain (s)	**COMPACTERS COS**	**ICHOM standard set**	**PIONEER COS for localised PCa**
Life impact; 25: Physical functioning AND 26: Social functioning AND 28: Emotional functioning/well being AND 30: Global 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)	Overall quality of life	Overall quality of life (including anxiety, depression, lack of confidence, feeling less masculine, feeling tired or fatigued, 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)

COMPACTERS = Core Outcome Measures for Prostate Cancer Effectiveness Trials; COS = core outcome set; HIFU = high-intensity focused ultrasound; ICHOM = International Consortium for Health Outcome Measurement; LUTS = lower urinary tract symptoms; PCa = prostate cancer.

terms (eg, "BCR") cannot capture every detail of such an outcome, but improving consistent reporting and use in analyses will increase power and precision, especially for big data sets. The same problems exist for the definition of each outcome. We were able to define two (updated) COS (Table 4 and Table 5) that should be used not only in future research but also in daily practice to improve standardised and structured medicine and prevent missing essential factors during follow-up for oncological patients.

This heterogeneity in PCa-related outcomes, the diversity in disease-related definitions, and the lack of consensus between different stakeholders prevent us from utilising the full potential of big-data sets. Standardisation of outcome terms and definitions will allow the extraction of relevant information from (multidisciplinary) big-data sets to inform guidelines and daily policy, which is the ultimate goal of the PIONEER project.

For our COS for localised PCa, no new outcomes were identified in comparison to the COMPACTERS COS and ICHOM standard set. This confirms the validity and clinical relevance of these reported outcomes. Although this clinical landscape might undergo some relevant changes (eg, studies on neoadjuvant treatment), these will probably not impact the identified outcomes. In light of future research, adherence to the core outcomes reported in our updated COS and the newly proposed consensus-based definitions for each core outcome should be recommended.

Second, we created a new COS for metastatic PCa for which we identified a total of eight new outcomes in comparison to the existing ICHOM standard set. As the treatment landscape for nmCRPC is still highly evolving, it is likely that new outcomes will be identified in the future. Moreover, for evaluation of patients with CRPC (metastatic or non-metastatic disease), for which new treatment strategies are frequently implemented, there is a need for a robust surrogate endpoint for overall survival for short-term evaluation. The ICECaP (Intermediate Clinical Endpoints in Cancer of the Prostate) initiative is evaluating these surrogate endpoints and the results will have implications for future COS.

Third, our patient interviews revealed that QoL issues such as fear of progression and dying are raised by patients and discussed in ways that convey the seriousness of the impact of these concepts on their life. Our results triangulate well with data reported in a meta-synthesis of qualitative studies that, although focussed on masculine identity, touched on many of the outcomes we also report [59]. Likewise, our data corroborate the EUPROMS quantitative study of health-related QoL in 2943 PCa patients from across the disease/treatment spectrum in 24 European countries [60,61]. The extent to which these concepts are adequately reflected in generic cancer PROMs or PROMs specific too metastatic PCa is currently unclear and will be addressed in the next phase of our research.

The ultimate goal of PIONEER is to successfully implement to use of our COS in daily clinical practice. We were able to integrate earlier COS work from ICHOM and COMPACTERS and achieve consensus on ClinRO definitions for localised PCa (Table 4) and on ClinRO definitions for the COS for metastatic PCa (Table 5). This delivers clarity on "what" and "how" to measure certain outcomes and reduce inconsistency and ambiguity during follow-up for both the clinician and the patient.

Major improvements can be achieved by consistently measuring and reporting outcomes across clinical trials and in observational studies for the same health condition and/or intervention. This will optimise our ability to compare and pool results from different trials and increase the statistical power and precision of meta-analyses, as this is often compromised by significant heterogeneity. There is a need for consistent reporting, especially in an era in which big data are increasingly used to answer clinically relevant questions. Implementation of our COS will still be a major challenge in terms of how to facilitate the uptake among potential users (both clinicians and patients). PIONEER has involved multiple stakeholders to make the COS as applicable as possible for both prospective and retrospective research and to promote them in publications and presentations at various international conferences. We recommend implementation of our COS (and their definitions) for RCTs, systematic reviews, clinical audits, clinical practice guidelines, and big-data projects.

We also converted the outcomes into operational definitions for database management and analyses of various diverse data sets. A first application occurred during our PIONEER study-a-thon, a focused event in which a large-scale study, which traditionally takes many months to complete, is executed and completed in a few days. We specifically investigated outcomes for men with PCa on watchful waiting using data sets with health care records for more than 1 million patients with PCa [62].

Table 2 – Organisation of outcomes within the 38-item Dodd taxonomy: original terms used in previous research and outcome terms decided on by PIONEER expert groups after two rounds of consensus meetings for the metastatic PCa setting

Core area(s); domain(s)	**ICHOM COS**	**Newly identified outcomes**	**PIONEER COS for metastatic PCa**
Death; 1: Mortality/survival	Overall survival		**Overall survival**
	Cause specific survival		**PCa-specific survival**
		Death from causes other than PCa	Not included after consensus meetings with patients and clinical experts
Physiological or clinical; 16: Outcomes relating to neoplasms	Development of metastasis		Not included after consensus meetings with patients and clinical experts
	Development of castration-resistant disease		**Development of castration-resistant disease**
		RECIST objective response rate	Not included after consensus meetings with patients and clinical experts
		Biochemical progression-free survival	**Biochemical progression-free survival**
		Radiographic progression-free survival	**Radiographic progression-free survival**
		Clinical progression-free survival	**Clinical progression free survival**
		PSA response	**PSA response**
		Time to prostate-specific antigen progression	Not included after consensus meetings with patients and clinical experts
		Bone progression-free survival rate	Not included after consensus meetings with patients and clinical experts
	Symptomatic skeletal event		**Symptomatic skeletal event**
Resource use; 66: Need for further intervention	Procedures needed for local progression		**Procedures needed for local progression**
	Need for pain medication		Not included after consensus meetings with patients and clinical experts
Physiological or clinical; 9: General outcomes	Pain (EORTC QLQ-C30)		**Pain**
	Fatigue (EORTC QLQ-C30)		**Fatigue**
Physiological or clinical; 8: Gastrointestinal outcomes	Bowel symptoms (EPIC-26)		**Bowel dysfunction**
Adverse events; 38: Adverse events/effects	Hormonal symptoms (EPIC-26)		**Side effects of systemic therapy**
Physiological or clinical; 20: Reproductive system and breast outcomes AND **Life impact**; 28: Emotional functioning/ wellbeing AND 25: Physical functioning	Sexual dysfunction (EPIC-26 + EORTC QLQ-PR25)		**Sexual dysfunction**
Physiological or clinical; 19: Renal and urinary outcomes	Urinary symptoms (EPIC-26)		**Urinary dysfunction**
Life impact; 28: Emotional functioning/ wellbeing	Emotional functioning (EORTC QLQ-C30)		**Emotional dysfunction**
Life impact; 25: Physical functioning	Physical functioning (EORTC QLQ-C30)		**Physical dysfunction**
Adverse events; 38: Adverse events /effects	Major systemic therapy complications		Not included after consensus meetings with patients and clinical experts
Life impact; 31: Perceived health status	Performance status (ECOG/ WHO)		**Performance status**

COS = core outcome set; ECOG = Eastern Cooperative Oncology Group; EPIC-26 = Expanded Prostate Cancer Index Composite-26; EORTC = European Organization for Research and Treatment of Cancer; HIFU = high-intensity focused ultrasound; ICHOM = International Consortium for Health Outcome Measurement; LUTS = lower urinary tract symptoms; PCa = prostate cancer; QLQ-C30 = Quality of Life Questionnaire-30 item; QLQ-PR25 = Quality of Life Questionnaire-Prostate Cancer module; RECIST = Response Evaluation Criteria in Solid Tumours; WHO = World Health Organization.

In addition to our work to provide definitions for each ClinRO contained within the COS, we have also critically appraised the measurement properties of PROMs used to assess the functional and health-related QoL outcomes within the COS and that have been used in studies on patients with PCa. This study is reported separately [17]. In brief, we identified which functional and QoL PROMs were used in RCTs and then assessed the methodological quality of each study on the development and evaluation of the PROM properties in accordance with the COSMIN risk-of-bias checklist for systematic reviews of PROMs. Following our assessment, we recommend the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-30 item (EORTC QLQ-C30) and Quality of Life Questionnaire-Prostate Cancer module (EORTC QLQ-PR25) [17,63].

Similar to the strategies for other big-data projects funded by the EU Innovative Medicines Initiative, we have provided COS for different stages of PCa that were developed in a process involving all relevant stakeholders for the first time. Nevertheless, these COS are never final. They represent an agreed minimum set of outcomes that can be

Table 3 – Outcomes identified in the systematic review for non-metastatic castration-resistant prostate cancer that were not captured in the core outcome sets for the metastatic setting

Study	Outcomes
ARAMIS; Fizazi 2019 [54]	**Time to initiation of subsequent antineoplastic therapy**
SPARTAN; Smith 2018 [57]	**Time to metastasis** (time from randomisation to first detection of distant metastasis involving the bone or soft tissue on imaging, as assessed via blinded independent central review)
	Time to symptomatic progression (time from randomisation to a skeletal-related event, pain progression, or worsening of disease-related symptoms leading to initiation of a new systemic anticancer therapy, or time to the development of clinically significant symptoms due to local or regional tumour progression leading to surgery or radiation therapy)
	Second progression–free survival (time from randomisation to investigator-assessed disease progression [prostate-specific antigen progression, detection of metastatic disease on imaging, symptomatic progression, or any combination thereof] during the first subsequent treatment for metastatic castration-resistant disease or death from any cause)

added to with defendable justification, depending on the clinical setting and changes in the treatment landscape. The value of an outcome rated as important may also differ by disease stage and where the patients are in the pathway. These treatment-specific needs can already be seen in the current COS, as some outcomes have different definitions depending on the treatment setting (eg, biochemical recurrence). Moreover, there are some limitations to the methodology that need to be pointed out. During our literature review, some RCTs may have been missed because we only included systematic reviews of RCTs. However, we carried out additional manual screening of the EAU 2021 guidelines to reduce this risk [1]. Another limitation is the exclusion of nonrandomised studies for the update, as we limited our inclusion criteria to RCTs. Nonetheless, work by the COMPACTERS group [11] has shown that the outcomes captured in RCTs reflect the outcomes identified in observational studies. The COS have been developed taking into consideration the European viewpoint, as most of the participants of the consensus meeting have been working in the European context; however, the literature reviewed was not limited to the European context.

Table 4 – PIONEER definitions for core outcomes for localised PCa using clinician-reported outcomes

PIONEER COS	Definitions	Consensus
1. Overall survival	Refers to death from any cause. Reported either at a defined time point (eg, 5 yr) or as time to event (depending on study design).	100%
2. PCa-specific survival	Refers to PCa-specific death. Reported either at a defined time point (eg, 5 yr) or as time to event (depending on study design).	100%
3. Biochemical recurrence	RP: two consecutive PSA rises ≥0.2 ng/ml. FT and EBRT: Phoenix criterion (nadir + 2 ng/ml) after local curative therapy (EBRT or FT).	100%
4. Local disease recurrence	RP: development of a palpable nodule on DRE, or pelvic lesion identified on imaging in conjunction with a detectable serum PSA level.	100%
	EBRT: abnormal DRE findings (change in DRE subsequent to initially becoming normal after treatment), Phoenix criterion (nadir + 2 ng/ml), positive imaging and/or residual disease on biopsy.	73%
	FT: any imaging, positive control biopsy (irrespective of the side) and/or salvage therapy.	100%
5. Distant disease recurrence/metastases	Development of distant metastasis on imaging.	86%
*		100%
7. Need for curative treatment (applicable to AS specifically)	Patients discontinued AS and underwent treatment for various reasons including change in patient preference, increasing PSA, DRE suggestive of more advanced features, biopsy evidence of increased tumour volume or higher grade, doctor's decision, with or without new findings on MRI.	100%
8. Treatment failure (applicable to ablative procedures [cryotherapy, HIFU])	HIFU (whole gland): any record of a positive prostate biopsy after HIFU, initiation of secondary prostate cancer treatment (eg, hormone therapy, second HIFU procedure, radiotherapy or surgery), radiographic evidence of prostate cancer metastases or prostate cancer-related death, PSA greater than test level or Phoenix criterion.	77%
	Cryotherapy: change in DRE, rising PSA, positive biopsy, or radiographic evidence of progression.	82%
9. *		100%
10. Positive surgical margins (surgery)	Positive when the tumour reaches the inked surface of the specimen	100%
11. Bowel dysfunction	Assessed using PROMs	
Faecal incontinence		
12. Urinary dysfunction	Assessed using PROMs	
Stress incontinence		
13. Sexual dysfunction	Assessed using PROMs	
14. Side effects of hormonal therapy	Assessed using PROMs	
15. Major surgical complications	RP: presence or absence of early (<30 d) or late (≥30 d) Clavien-Dindo grade 3–5 complications	86%
Perioperative death (surgery-specific)		
Thromboembolic disease (surgery-specific)		
Bothersome or symptomatic urethral or anastomotic stricture (surgery-specific)		
16. Radiation toxicity/major radiation complication	EBRT: presence or absence of acute (<90 d) or late (≥90 d) radiation toxicity as defined in a validated tool (eg, RTOG, LENT/SOM)	91%
17. Overall quality of life	Assessed using PROMs	

AS = active surveillance; DRE = digital rectal examination; EBRT = external beam radiation therapy; FT = focal therapy; MRI = magnetic resonance imaging; PCa = prostate cancer; PROMs = patient-reported outcome measures; PSA = prostate-specific antigen; RP = radical prostatectomy.
* There was a consensus vote to exclude this outcome because of repetition of measurement.

Table 5 – PIONEER definitions for core outcomes for metastatic PCa using clinician-reported outcomes

PIONEER COS	Definition	Consensus
1. Overall survival	Refers to death from any cause. Reported either at a defined time point (eg, 5 yr) or as time to event (depending on study design).	–
2. PCa-specific survival	Refers to death from prostate cancer. Reported either at a defined time point (eg, 5 yr) or as time to event (depending on study design).	–
3. Development of castration-resistant disease (only applicable to hormone-sensitive PCa)	Castrate level of serum testosterone <50 ng/dl or <1.7 nmol/l plus either a. Biochemical progression: Three consecutive rises in PSA 1 wk apart resulting in two 50% increases over the nadir, and PSA >2 ng/ml OR b. Radiological progression: Appearance of new lesions (either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST). Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose castration-resistant PCa.	73%
4. Biochemical progression-free survival	Castrate serum level of testosterone <50 ng/dl or <1.7 nmol/l plus Biochemical progression: three consecutive rises in PSA 1 wk apart resulting in two 50% increases over the nadir, and PSA >2 ng/ml.	100%
5. Radiographic progression-free survival	Radiological progression is the appearance of new lesions: either two or more new bone lesions on imaging or a soft tissue lesion using RECIST, ideally through central review.	100%
6. Clinical progression-free survival	Time to the first occurrence of symptomatic skeletal related events, pain, or other symptoms, objective evidence of an increase in extent of disease or death.	90%
7. PSA response	Reduction in the PSA level from baseline by ≥50% or ≥90%, as confirmed on an additional PSA evaluation performed ≥3 wk later and patients at castrate level (if on ADT).	100%
8. Procedures needed for local progression	Could be one of the following procedures: – Transurethral resection of the prostate – Ureteral stent – Percutaneous nephrostomy tube – Suprapubic catheter placement – Chronic Foley catheter – Intermittent self-catheterisation – Extensive pelvic surgery – Palliative radiotherapy	100%
9. Symptomatic skeletal event	Symptomatic fracture, cord compression, or need for surgery and/or radiation to bone	85%
10. Bowel dysfunction	Assessed using PROMs	
11. Side effects of systemic therapy	Assessed using PROMs	
12. Sexual dysfunction	Assessed using PROMs	
13. Urinary dysfunction	Assessed using PROMs	
14. Emotional dysfunction	Assessed using PROMs	
15. Physical dysfunction	Assessed using PROMs	
16. Pain	Assessed using PROMs	
17. Fatigue	Assessed using PROMs	
18. Performance status	Assessed using PROMs	

ADT = androgen deprivation therapy; COS = core outcome set; HIFU = high-intensity focused ultrasound; PCa = prostate cancer; PROMs = patient-reported outcome measures; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumours.

4. Conclusions

These integrated COS for localised PCa, locally advanced PCa, metastatic PCa, and nmCRPC will be used by the PIONEER Consortium as a basis for data harmonisation across diverse big-data resources. To limit heterogeneity across research, they should be recommended for future effectiveness trials, systematic reviews, guidelines, and clinical practice for localised and metastatic PCa.

Author contributions: Katharina Beyer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: None.

Obtaining funding: PIONEER Consortium.

Administrative, technical, or material support: Beyer, Smith, Moris, Lardas, Omar, Flaherty, Devecseri, Lam, Williamson, Heer, S.J. MacLennan, Briganti, S. MacLennan, Van Hemelrijck.

Supervision: Omar, Zong, S.J. MacLennan, Briganti, S. MacLennan, Van Hemelrijck.

Other: None.

Financial disclosures: Katharina Beyer certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria,

stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** PIONEER is funded through the IMI2 Joint Undertaking and is listed under grant agreement 777492. This joint undertaking receives support from the European Union Horizon 2020 research and innovation programme and EFPIA. The views communicated within are those of PIONEER. Neither the IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained herein. .

Acknowledgement

We are grateful to all the patients and health care professionals who took part in our interview studies and to the patient representatives and advocates who provided insight during our various consensus meetings. We thank Dr. Susie Dodd for her advice on applying the 38-item outcome taxonomy that she and her COMET colleagues developed, and we accept responsibility for any (mis)application.

Peer Review Summary

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2022.01.042.

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