HTA assessment of quality of survival via patient-relevant endpoints in prostate cancer

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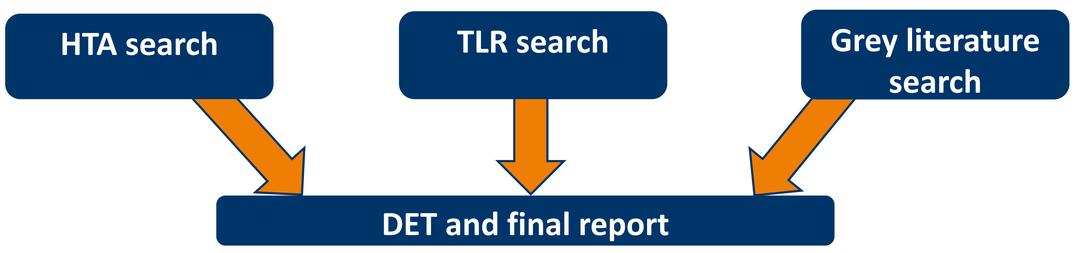
Introduction

> The use of patient-reported outcome (PRO) endpoints in clinical trials has increased significantly over recent years, especially in oncology, where therapeutic agents are known to contribute to high treatment burden.[1]
> Survival-related endpoints, such as the traditional oncology endpoint overall survival (OS), are typically favoured by Health Technology Assessment (HTA) bodies and payers. However, OS data do not provide insight into the quality of patient survival.[2] Further, the investment required to gather mature OS data, in terms of both cost and time, is challenging and may delay patients' access to new medicines.
> Several well-established PRO measures have been developed in oncology and haematology to assess a patients' symptoms and quality of life at a point in time. However, there is a need for HTA bodies to consider novel patient-relevant endpoints which assess patients' experiences in combination with progression of disease.
> The aim of this research was to identify and review published literature relating to novel patient-relevant endpoints in oncology, using prostate cancer as an example, to determine HTA bodies' use and acceptance of these endpoints.

Methods

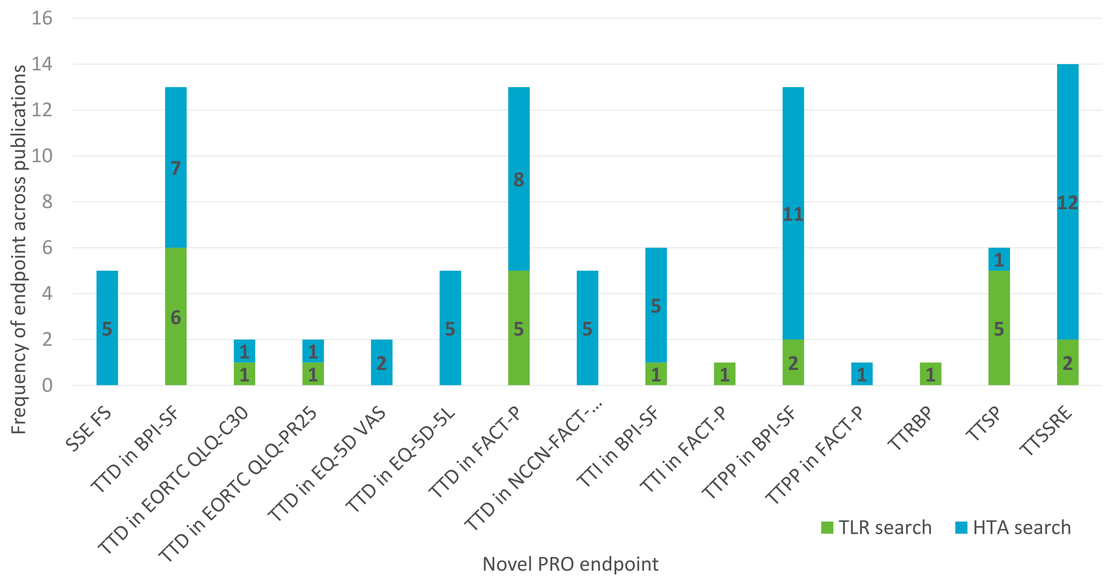
> For this landscape review, two researchers completed an initial review of therapies approved for prostate cancer in the past three years (2021–February 2024), across 10 regulatory and HTA bodies (across Canada, Europe and the United States). These findings informed the search strategy for a targeted literature review (TLR).
> The TLR search was conducted in February 2024 using the OVID platform to search the Embase, Medline® and PsychINFO databases for the past three years (2021–February 2024) with specific terms relating to novel patient-relevant endpoints in prostate cancer.
> For the TLR, abstracts and full-texts were screened by one reviewer (quality check completed by a senior reviewer) and rationale for inclusion or exclusion was based on the pre-defined PICOTS criteria. Literature reporting on novel patient-relevant endpoints utilised in clinical trials in prostate cancer were included.
> The TLR was supplemented by a grey literature search of four congresses (International Society for Pharmacoeconomics and Outcomes Research [ISPOR], European Society for Medical Oncology [ESMO], American Society of Hematology [ASH], and European Haematology Association [EHA]) from the past three years (2021–February 2024).
> The findings from the regulatory, HTA, TLR and grey literature searches were captured in a data extraction table (DET), including the novel patient-relevant endpoint definition and threshold, and opinion related to its use, and were summarized in the final report.



Results (continued)

> Overall, 41 publications and appraisals on novel patient-relevant endpoints in prostate cancer were identified. The HTA search identified 23 appraisals, while the TLR and grey literature searches identified 17 publications (which reported on 12 studies).
> Overall, 15 novel patient-relevant endpoints were identified that capture patient experiences with prostate cancer (Figure 1).
> The most common patient-relevant endpoint identified across the HTA appraisal documents was time to symptomatic skeletal-related event (TTSSRE). The most frequently identified novel PRO endpoint in the TLR search was TTD in BPI-SF.

Figure 1. Number of novel PRO endpoints identified across publications and appraisal documents for prostate cancer



BPI-SF: Brief Pain Inventory-Short Form Questionnaire; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module; ; EQ-VAS: EQ visual analogue scale; ; EQ-5D-5L: The EuroQol 5 Dimension 5 Level; FACT-P: Functional Assessment of Cancer Therapy- Prostate Questionnaire; NCCN-FACT-FPSI-17: National Comprehensive Cancer Network - Prostate Symptom Index Questionnaire - 17 items; PRO: Patient reported outcome; SSE-FS: Symptomatic skeletal event free survival; TTD: Time to deterioration TTI: Time to improvement; TTPP: time to pain progression TTRBP: Time to radiographic bone progression; TTSP: Time to symptomatic progression; TTSSRE: Time to symptomatic skeletal related event.

*Frequency of endpoint may exceed the number of publications due to some reporting >1 endpoint.

Results (continued)

> **Time to symptomatic skeletal-related event (TTSSRE) and symptomatic skeletal-related event free-survival (SSE-FS):**
  - TTSSRE and SSE-FS endpoints measure the duration a patient remains free from SSEs and are useful endpoints for cancers which frequently metastasize to the bone, such as prostate cancer.
  - Generally positive HTA opinions were identified for both TTSSRE and SSE-FS. These were often considered patient-relevant endpoints which translate into meaningful benefits.[3-6]
  - HTA appraisals citing TTSSRE and SSE-FS generally recommended the products assessed and these endpoints were often referred to in the rationales for product acceptance.

Table 1. Number of HTA appraisals and opinions on TTSSRE and SSE-FS in prostate cancer

	NICE	SMC*	G-BA*	IQWiG*	CADTH
TTSSRE	NA	2 ✓	2 ✓	2 −	1 ?
SSE-FS	1 ✓	1 −	1 ✓	1 ✓	1 −

*Three appraisals from SMC, G-BA and IQWiG mentioned but did not give opinions on these endpoints.
NA; not reported (no appraisals utilising this endpoint were identified).

✓ Positive − Neutral ? Unknown

> **Time to deterioration (TTD):**
  - TTD provides useful insight into the patients' subjective appreciation of different treatments and the impact they had on quality of life (QoL).[7]
  - There was no consistently applied definition or threshold used for TTD endpoints, regardless of PRO tool used.
    - One HTA appraisal gave a positive opinion on the use of time to first deterioration in BPI-SF and FACT-P when assessing a prostate cancer therapy.[8] However, this endpoint did not dictate the product recommendation.
    - Five HTA bodies gave neutral opinions for TTD in the FACT-P questionnaire and TTD in BPI-SF for prostate cancer.

Table 2. Number of HTA appraisals and opinions for TTD in prostate cancer

	NICE	SMC*	G-BA	IQWiG	CADTH
Time to **first** deterioration in BPI-SF and FACT-P	NA	NA	1 ✓	1 −	NA
TTD in BPI-SF and FACT-P	1 −	2 −	1 −	1 −	1 −

*One additional appraisal from SMC mentioned but did not give opinions on these endpoints.
NA; not reported (no appraisals utilising this endpoint were identified).

✓ Positive − Neutral

> **Time to symptomatic progression (TTSP):**
  - This is a composite measure of worsening symptoms in combination with disease progression, which is clinically relevant in advanced disease settings such as prostate cancer.[9]
    - However, TTSP was frequently not defined across literature and did not have a consistently applied quantitative threshold.
  - Only one HTA appraisal utilised the TTSP endpoint in prostate cancer. The appraisal recommended the product under investigation (niraparib and abiraterone acetate), highlighting this may result in a clinical benefit in TTSP, although caveated low certainty due to concerns for imprecision and limitations in the trial.[10]

HTA body	TTSP threshold / definition	Opinion
CADTH	Measured using FACT-P	−

Conclusions

> The necessity for patient-relevant endpoints that provide an indication of a patient's quality of survival which can be measured within a shorter time period than OS data has become increasingly evident.
> The literature demonstrated that novel patient-relevant endpoints are currently used within prostate cancer trials, and some are positively reviewed by HTA, although the need for standard definitions was highlighted regardless of PRO tool used, and the relevance of each to different patient subgroups needs to be assessed.
> There are potential benefits in exploring the use of similar endpoints within clinical trials for oncology indications and assessing HTA opinion on the value of novel endpoints relative to OS.

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