Prostate cancer is the most common male cancer in the UK. In 2012, 43,400 men were diagnosed with and 10,800 men died from this cancer in the UK. It has been estimated that approximately 10% of men diagnosed with prostate cancer present with advanced or metastatic disease. In addition, other men relapse and progress to develop advanced disease after initial radical treatment for localised or locally advanced disease. Advanced prostate cancer can be associated with debilitating symptoms, including metastatic bone pain, fracture and spinal cord compression, in addition to local symptoms from the primary tumour.

Initial treatment for advanced prostate cancer is with androgen deprivation therapy (ADT), which is achieved by either orchiectomy or, more commonly, by chemical castration using luteinising hormone-releasing hormone agonists (LHRHa). In the majority of patients, ADT achieves remission and delays disease progression. However, disease-related symptoms, in addition to toxicities from ADT and the psychological impact of living with advanced disease, remain a clinical challenge.

Survival remains a primary aim of treatment in prostate cancer, but quality of life is also an essential benefit of any therapy. Patient-reported outcome measures, which record quality of life as perceived by the patient, are now widely used in cancer trials and, as discussed in this article, have a place in everyday practice.

Figure 1. EPIC is a well-established PROM questionnaire developed to monitor HR-QOL outcomes in prostate cancer survivors (http://medicine.umich.edu/dept/urology/research/epic)
with an ‘incurable’ cancer, can have a significant impact on health-related quality of life (HR-QOL).

Following the initial benefits of ADT, men invariably progress with resistant disease (castration-resistant prostate cancer – CRPC). Historically, further treatment modalities have been limited, but this has changed over the last decade as a number of new and exciting chemotherapy, bone-targeted and novel hormonal agents have demonstrated significant increases in overall survival (OS) for men with progressive metastatic CRPC.2-4

The optimal management and sequencing of these drugs is an increasingly complex process, involving many different disciplines in primary, secondary and palliative care and, most importantly, the specific needs, views and circumstances of each individual patient and consideration of how therapy will affect their HR-QOL.

Survival remains a primary measure of treatment effect, but HR-QOL is also an essential component of the overall benefit of any therapy. Patient-reported outcome measures (PROMs) instruments, collecting information on HR-QOL as perceived by the patient himself, are now widely used in cancer treatment trials and have future implications for our everyday practice.

WHAT ARE PROMS?

Questionnaires may be self-administered or administered at point of care. A large number of validated questionnaires assessing HR-QOL for specific diseases have been developed by different groups and disciplines. Disease-specific PROMs are often used in randomised control trials to assess a range of relevant health domains and to monitor real-life consequences of treatment.

The most frequently used PROMs for metastatic prostate cancer are discussed in this review, including EPIC, FACT-P, EORTC QLQ-C30 and EQ-5D PROMs.5

**Expanded prostate cancer index composite (EPIC)**

EPIC is a well-established PROM questionnaire developed to monitor HR-QOL outcomes in prostate cancer survivors (Figure 1). EPIC has been shortened and refined in recent years to make it easier for patients to complete. The EPIC-50 was derived from the UCLA Prostate Cancer Index and contains 50 items assessing five prostate cancer-specific domains: urinary incontinence; urinary irritation/obstructive symptoms; bowels; sexual; and vitality/hormonal.6

The original version was time-consuming to complete, which limited its use outside of clinical trials. A shorter version, the EPIC-26, was therefore designed. This evaluates the same five symptom domains as the EPIC-50, but consists of only 26 questions and takes between 10 and 15 minutes to complete, scoring from worst (0) to best (100). EPIC-26 is a useful tool to monitor domain-specific changes in HR-QOL among prostate cancer survivors over time, and can quantify changes resulting from the introduction of new treatments.1 A working group for the International Consortium for Health and Outcome Measurements (ICHOM) has recently recommended EPIC-26 as a valuable tool for the standardised collection of data across different centres to allow internationally comparable collection of PROMs after treatment for localised prostate cancer.8

The Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) was developed for routine clinical care of patients with prostate cancer. Shorter and more practical for community and academic purposes, it is a one-page, 16-item questionnaire, which aims to improve the collection and management of patient-reported outcomes outside of clinical trials and may be used or adapted to collect data in the clinic setting.9

**BROADER PROMS TOOLS**

Men diagnosed with metastatic disease frequently experience symptoms outside urinary, bowel and sexual domains that have an impact on their QOL. These include mood symptoms/psychological changes and pain. Tools addressing general HR-QOL for advanced disease include the FACT-G, EORTC-QLQ-C30 and EQ-5D, which have been validated specifically in patients with cancer and used in trials in metastatic prostate cancer.10,11

The Functional Assessment of Cancer Therapy – Prostate Scales (FACT-P)
The Functional Assessment of Cancer Therapy – General (FACT-G) was developed in the USA and, since 1989, has been widely utilised in cancer studies for the assessment of HR-QOL FACT-G requires 8–10 minutes to complete, and includes 39 questions involving four domains: physical, functional, social and emotional. Multiple subscales have been added for different tumour types. FACT-P is a well-validated, self-administered questionnaire used specifically in prostate cancer, which includes the FACT-G scale and a prostate cancer subscale (PCS) (Figure 2). The PCS addresses issues related to sexuality, bowel/bladder function and pain. Higher scores indicate higher HR-QOL, and an increase of greater than five points indicates significant improvement in HR-QOL.11

The FACT-P tool is validated in all stages of prostate cancer. Patients with advanced prostate cancer consistently score lower on FACT-P compared with patients with localised disease, reflecting the physical and psychological effects of increased disease burden and perhaps the toxicities of additional therapies. FACT-P was also found to be sensitive to changes in other indicators of treatment efficacy, including performance status and PSA levels.11

The European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQ-C30)
The EORTC-QLQ-C30 is another commonly used questionnaire. Designed to assess the QOL of all cancer patients participating...
in clinical trials and widely used in prostate cancer research, it includes nine multi-item scales: five scales include physical, role, cognitive, emotional and social; three scales focus on symptoms (fatigue, pain, nausea and vomiting); and there is a single global health and QOL scale.\textsuperscript{13,14}

**EuroQol (EQ-5D)**

In response to the vast number of QOL measures available, the EuroQol Group created the EQ-5D questionnaire. This has been designed as an international, standardised, generic instrument for describing and evaluating HR-QOL, to allow comparison of QOL measures between different studies and diseases. It is non-disease specific and includes six dimensions of health mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with one question per domain. It is short, self-administered and developed for ease of use outside of clinical trials.

In advanced prostate cancer trials where the EQ-5D has not been measured, models have been developed to 'translate' prostate cancer-specific HR-QOL using results from FACT-P and EORTC-QLC-C30 scores, in order to obtain a single index value for EQ-5D. EQ-5D can also be used to evaluate cost-effectiveness.\textsuperscript{10}

**ANALGESIC SCORES**

Pain is one of the most common symptoms in advanced prostate cancer and several pain assessment questionnaires are routinely used in prostate cancer trials.

The Brief Pain Inventory (BPI) was initially developed to assess pain related to cancer. The BPI pain intensity scale has four questions to capture the variability of pain over time. A visual analogue scale is used, with a range of 0–10 (where 0 equals no pain and 10 is pain as bad as you can imagine). Pain is rated when it is at its worst, least, average and right now (Figure 3). In patients with advanced prostate cancer, the BPI score demonstrates stability over time and corresponds with other aspects of patient-reported health and clinical outcomes.\textsuperscript{15}

The Present Pain Intensity score (PPI) is a single question of the McGill Pain Questionnaire, which asks patients to characterise their present pain using descriptors from 0 (no pain) to 5 (excruciating). There is little literature comparing the psychometric performance of these pain scales in prostate cancer. However, the BPI pain intensity and FACT-P pain scales may be better than the PPI question at capturing the pain experience among patients with advanced prostate cancer.\textsuperscript{16}

Many patients with advanced prostate cancer use analgesic medications for their pain. The World Health Organization Analgesic Treatment Ladder has been used to quantify analgesic medication use among patients with advanced cancer in several trials. The Analgesic Quantification Assessment (AQA) represents a sensitive measure of analgesic use and may better determine whether changes in pain assessments in clinical trials are due to the intervention or changes in analgesic use.

To determine the initial AQA score each patient is scored by the World Health Organization Analgesic Ladder. The score is then converted into a daily Oral Morphine Equivalent (OME). The results score on the 8-point AQA scale corresponds to no analgesic use, non-opioid analgesics, weak opioids and strong opioids (Table 1).\textsuperscript{17}

Changes in pain scores can be a good indicator of the efficacy of both the analgesic used and specific cancer drugs in reducing the burden of metastatic disease.

**PROMS IN RECENT TRIALS IN CRPC**

Overall survival and progression-free survival are relevant and important primary
endpoints in many randomised controlled trials in metastatic CRPC. However, they do not provide a comprehensive picture of overall treatment effects. The QOL for each individual patient will be different, as each person has different expectations and goals in life that cannot be predicted by clinicians. The increasing importance of PROMs as a clinical endpoint is now widely recognised, with several recent trials evaluating the effectiveness of drugs in CRPC collecting QOL measures as secondary endpoints.\textsuperscript{2,3,18}

An example of the incorporation of PROMs in a clinical trial is the COU 302 study, where 1088 asymptomatic or mildly symptomatic men with progressive CRPC without prior chemotherapy were randomised to receive the novel hormonal agent abiraterone (Zytiga) 1000mg/day plus low-dose prednisolone (10mg daily) or placebo plus prednisolone. The final analysis of this trial, after a median follow-up of 49.2 months, showed a significant improvement in median OS in favour of abiraterone and prednisolone group. The study also reported benefits in the delay in median time to opiate use, from 23.4 months for prednisolone to 33.4 months in the abiraterone and prednisolone combination.\textsuperscript{2}

A WIDER ROLE FOR PROMS
There are a large number of PROMs tools available, and differences between them can make it difficult to directly compare outcomes in different trials. However, standardised PROMs in advanced disease enable the collection of meaningful and internationally comparable outcomes on QOL, which can inform clinical decision-making and funding. Recently, the ICHOM panel of experts identified relevant measures of HR-QOL to form recommendations for a standard set of patient-centred outcomes in APC. It recommended two questionnaires, as it felt no single tool sufficiently covered all relevant domains: a prostate cancer-specific questionnaire, EPIC, to assess sexual, urinary, and hormonal and bowel function, and an overall QOL questionnaire, the EORTC QLQ-C30 instrument, for cancer-related QOL.\textsuperscript{19}

Doctors frequently underestimate the effects of disease and its treatment on patients' QOL.\textsuperscript{20} PROMs facilitate the collection of comprehensive information regarding HR-QOL, which better enables doctors to consider not only overall and progression-free survival, but how treatments affect an individual patient in daily life. The QOL changes documented may result from changes in

<table>
<thead>
<tr>
<th>AQA Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No analgesic</td>
</tr>
<tr>
<td>1</td>
<td>Non-opioid analgesic</td>
</tr>
<tr>
<td>2</td>
<td>Weak opioids*</td>
</tr>
<tr>
<td>3</td>
<td>Strong opioids ≤75mg OME per day</td>
</tr>
<tr>
<td>4</td>
<td>Strong opioids &gt;75–150mg OME per day</td>
</tr>
<tr>
<td>5</td>
<td>Strong opioids &gt;150–300mg OME per day</td>
</tr>
<tr>
<td>6</td>
<td>Strong opioids &gt;300–600mg OME per day</td>
</tr>
<tr>
<td>7</td>
<td>Strong opioids &gt;600mg OME per day</td>
</tr>
</tbody>
</table>

Table 1. Analgesic Quantification Algorithm scoring system (AQA, Analgesic Quantification Algorithm; OME, oral morphine equivalent)
burden of disease, treatment toxicity and psychological factors.

Although PROMs questionnaires are now widely used in clinical trials, they are not widely used in routine clinical practice. Some tools are multi-dimensional and difficult to administer, which limits their use to clinical trials. The development of less time-consuming and easier to administer questionnaires should encourage the wider use of these tools and may improve everyday practice. Additionally, smartphones and wider access to the internet may improve the distribution of PROMs tools, allowing for the real-time collection of HR-QOL data, resulting in better shared decision-making between doctors and their patients.

CONCLUSION
Metastatic prostate cancer is an incurable disease and patient QOL is of the utmost importance. Historically, the collection of data on patients’ own perspectives on their QOL was poor. However, the incorporation of tools in both clinical trials and routine practice in the clinic setting can provide valuable QOL information. Thanks to the development of PROMs, patients now have a voice in the development and assessment of new therapeutic strategies in metastatic prostate cancer.

Declaration of interests
Heather Payne has attended and received honoraria for advisory boards, travel expenses to medical meetings and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Amgen, Ipsen, Ferring and Novartis. Her work was supported by the UCLH/UCL Comprehensive Biomedical Research Centre.

REFERENCES