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The importance of patient-reported outcomes in cancer studies

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The importance of Patient-Reported Outcomes in cancer studies

1. Abstract

Introduction: Cancer incidence is increasing; one in two people in the UK are expected to develop cancer during their lifetime. However, survival rates of people living with cancer have improved over the last few decades. More than 50% of all UK cancer patients survive for beyond 10 years, this rate has doubled in the last 40 years.

Areas covered: This article provides a scientific review of the use of patient reported outcomes (PROs) to assess the short and longer term impact of cancer and treatment on patient quality of life and symptoms.

Expert opinion/commentary: There is increasing recognition that, in addition to survival and other clinical metrics, we need to understand more about the impact that cancer and its treatment has on the everyday lives of people living with and beyond cancer. Patients must have access to information around quality of life and survival with which they can make more informed decisions about their care. We need to understand more about the natural history of recovery and wellbeing and the contributory factors to identify those who are not doing well and to understand how we can support them better, plan appropriate services and support patients in making choices about treatment.

2. Introduction

The incidence of cancer is increasing; it is now expected that one in two people in the UK will develop cancer at some point in their lives[1]. The survival rates of people living with cancer have improved over the last few decades. More than 50% of all cancer patients in the UK are surviving for beyond 10 years, this rate has doubled in the last 40 years[2]. These improvements have been attributed to improved screening, earlier diagnosis and enhancements in, and access to, treatment. There are now 2.5 million people in the UK living with and beyond cancer[3]. The number of cancer survivors in the UK is projected to increase by approximately one million per decade (3% every year) resulting in four million people living with cancer in 2030[3].

There is increasing recognition that, in addition to survival and other clinical metrics such as toxicity grading, we need to understand more about the impact that cancer and its treatment has on the everyday lives of people living with and beyond cancer. Patients must have access to information around quality of life and survival in tandem, with which they can make more informed decisions about their care[4]. People can experience a range of issues following a cancer diagnosis, during and

beyond treatment, such as problems with social relationships, poorer quality of life, psychological distress, disease recurrence and progression, physical symptoms and financial consequences[5-8]. The impact these issues can have on patients is variable; some people do well after cancer treatment and some experience short, medium and long term consequences. We need to understand more about the natural history of recovery and wellbeing and the contributory factors in order to identify those who are not doing well and to understand how we can support them better, plan appropriate services and support patients in making choices about treatment (or having no treatment). One way to assess the short and longer term impact of cancer and treatment on patient quality of life and symptoms is through the use of patient reported outcomes (PROs). PROs may be used in addition to traditional clinical data to supplement clinical findings and attain a holistic understanding of patients' status.

Patient reported outcome measures (PROMs) are standardised, validated questionnaires that are completed by patients to measure their perceptions of their own functional status and wellbeing. They can be used to measure patients' perceptions of their general health or in relation to specific diseases or conditions[9]. As such, PROMs can focus on physical symptoms, treatment toxicities, psychosocial problems or global health-related quality of life (HRQoL) and many other relevant constructs[10]. PRO capture ensures the patients' experience of cancer and treatment is represented in health measurement and when considering the effectiveness of clinical interventions [11, 12]. Common non-cancer specific measures include the five dimension EuroQol questionnaire, the EQ-5D[13] and the Hospital Anxiety and Depression Scale, the HADS[14]. Commonly used cancer-specific measures include the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire[15] and the Functional Assessment of Cancer Therapy scale[16].

This article aims to provide a review of the use of PROs to assess the short and longer term impact of cancer and treatment on patient quality of life and symptoms. This is discussed first in the context of cancer research, then in routine cancer care, and lastly the next steps for PROs in cancer are considered.

3. PROs in Cancer Research

In cancer research, PROMs are used to measure the participants' assessment of the impact of a treatment or intervention upon their health condition, without interpretation of by a clinician or anyone else[17]. The complementary nature of PRO data when used in addition to other outcomes in trial settings has been demonstrated. It has been found that patients' reports better reflect daily health status and clinicians' assessments better predict unfavourable clinical events. When used in combination, both forms of data provide clinically pertinent information that warrants their inclusion in a trial[18]. PRO data collected in cancer studies can inform future patient choice and clinical decision-making, health technology assessment, health economic evaluations, labelling claims and healthcare policy and commissioning[19-21]; however this requires high quality PRO study design, rigorous data collection and appropriate reporting.

Patients are motivated to participate in clinical research due to the possibility of accessing a better form of treatment or that the trial results may benefit others[22-23]. Ethical practice in research dictates that data provided by participants is collected and reported to effectively contribute to the knowledge and practice in the field [24]. However, research suggests that the collection of PROs from participants is often inconsistent, creating a potential source of bias in the resulting data[25]. In

addition to this, a review of Health Technology Assessment trials funded by the National Institute for Health Research found that PRO-related information is commonly omitted from trial protocols, even where a PRO is the primary outcome, which may result in impaired data collection and poor quality data[26]. This was reiterated by the most recent study of its kind, the EPiC study[27], which in its review of the cancer clinical trials on the UK National Institute for Health Research portfolio found that studies on average included less than one third of the recommended PRO-related items for study protocols[28], replicating findings from an earlier Australian study[29]. In terms of reporting, a growing body of research suggests that PRO findings from cancer clinical trials are poorly reported by investigators in peer-review publications or not at all[30-32]. The EPiC study findings indicate that more than one-third of trials fail to publish PRO data, despite having reported findings related to the primary outcome[28]. Suggestions for future research regarding the collection, analysis and reporting of PRO data are explored in Box 1.

Box 1: Further questions for research, how is PRO data collected, analysed, and reported?

- Do terms such as, *quality of life* and *psychosocial outcomes,* need to be defined better in the research setting so that they can be measured and collected more effectively? In practice, these terms can be used interchangeably.
- How can we best identify outcomes of importance from the patients' perspective – so these can be incorporated in studies?
- How can PROs, such as QoL and psychosocial outcomes, be elevated in importance within a trial context when they are often chosen as secondary or exploratory objectives, following overall survival as primary? The quality of survival is overlooked.
- How can we facilitate the rapid analysis of PRO data so that the results can be interpreted alongside key clinical data such as survival?
- How can the wider infrastructure promote and support long-term collection and dissemination of PRO data? This might require a change of funding strategy by funding bodies.

Concerns about quality of data and poor reporting have clear implications for research findings reaching the necessary stakeholder groups, such as patients, clinicians, policy-makers and other researchers. Within these circumstances, the extent to which it may inform decision-making and changing practice is limited. Questions for future research relating to the use and dissemination of PRO data are presented in Box 2.

Reporting and disseminating research findings are undertaken for several reasons and via numerous channels[33]. Publication of research via the peer-review process with the aim of informing academic audiences is one step in the dissemination processs[34]. However, for research findings to reach wider audiences and have greater impact[35], different strategies must be pre-planned and implemented[36-38]. Unfortunately, there are few established outlets for the publication of PRO data which are easily accessible by cancer patients and clinical groups.

Challenges encountered in the collection of PRO data may be addressed through the use of PRO specific guidelines to aid in the design and planning of cancer studies. Good research conduct and reporting may be upheld through the use of guidelines supporting high quality study protocols[36]. In

addition to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement, providing a list of items recommended for inclusion in trial protocols[39], the recently developed SPIRIT PRO Extension[40] details additional PRO-specific items recommended to facilitate the effective incorporation of PROs in trial design. However, for such guidelines to have an impact, widespread endorsement is necessary by, for example, funders, journals and regulators. In relation to reporting, regulatory bodies may also have a role in ensuring the complete publication of trial findings. An example of this is a yet to be adopted directive by the EU for results for all trial endpoints to be published within one year of trial completion[41]. International guidance for the transparent reporting of PRO data, the CONSORT-PRO extension[42], may also be used by investigators and authors to aid in the quality and completeness of reports of PRO findings.

Box 2: Further questions for research, how is PRO data used and how could it be disseminated further?

- How can PRO data be incorporated more robustly in appraisals of new drugs or technologies – for licencing or in the UK NICE approval?
- How does PRO data affect clinical practice on a daily basis in terms of its implementation, impact and any subsequent improvements in care?
- How do patients currently access/use PRO data? Participants say, "Our data, our lives, how are we using it?"
- To what extent are patients currently involved in the dissemination process post-study? Is there a role for patients in championing findings and bringing PRO results to a broader audience?
- How might clinicians be encouraged to refer to PRO data to inform clinical practice and become consumers of this information? Are there currently under-used channels available or should new pathways be generated?

Beyond the immediate barriers to reporting, the changing global research setting may have as yet undetermined impacts upon the ongoing generation of PRO research, reporting and data use. An example of this is the case wherein the United Kingdom is poised to leave the European Union (EU), potentially posing barriers to continued data sharing[43] and collaboration in the field of cancer care and research[44]. Secure cross-country data sharing underpins international research particularly for conditions such as rare diseases and paediatric cancers where small numbers require statistical power to be attain via use of an international sample[45].

The research landscape is also changing in such a way that may lead to a paradigm shift in terms of the focus of cancer studies. Significant progress in cancer survival in certain cancer types[46] may shift focus from overall or progression-free survival to quality of survival[47] in some areas. Data pertaining to the quality of survival for those living with and without cancer would underpin such work and the concept of "quality of survival" would need to be embedded in clinical trials and studies for this purpose.

4. PROs in Routine Cancer Care

PROs are being increasingly used as a component of routine practice. Their use in clinical settings has been associated with richer discussions of patient outcomes, improved symptom control, increased supportive care responses, patient satisfaction and wellbeing[48, 49]. While findings suggest that PRO data may predict prognosis in cancer clinical trials[50, 51], research also indicates that their use in symptom monitoring during routine treatment is associated with increased survival compared with usual care[52].

It is well established that cancer patients value information relating to treatments and their risks and benefits[53, 54], and that such information aids patients in clarifying their treatment preferences[55-57]. For clinicians, PRO data may help facilitate patient-centred care[58, 59], bridging patients' concerns with their own[60]. As part of routine use in a clinical setting, PROMs can enhance the interaction between the healthcare provider and the individual, bringing about information due to the posing of questions that the clinician would not normally ask and topics that patients may not have chance to raise in a standard consultation. Using PROMs in routine practice can help increase the frequency with which issues related to health-related quality of life are discussed in consultations[49, 61]. These conversations can be sustained by the continued generation and reporting of PRO data in relation to treatments and interventions, providing answers to questions relating to how areas such as HRQoL might be addressed. PROs are increasingly being used as a means of patient surveillance and symptom monitoring during their receipt of care to promote overall survival and management of adverse events[62-64].

5. Where Next for PROs in Cancer?

The potential use of PROs in clinical settings is becoming a topic of increasing interest. In England, the Independent Cancer Taskforce in their strategy for achieving better cancer outcomes have included the development of a quality of life metric to monitor and support people living with and beyond cancer[65]. To this end, England will be the first country to routinely collect quality of life data from recovering cancer patients[66]. This represents a new approach to improve care through the use of personalised plans informed by data relating to their needs in addition to the physical aspects of health, moving quality of life data to the heart of commissioning decisions. Within this model, psychosocial risk stratification could be used to direct individuals into specialised services that address needs.

Emphasis on patient-centred care is also reflected in national cancer policy and expectations of practice. In England, the National Cancer Patient Experience Survey focused on areas pertaining to patients' perception of their understanding and involvement in treatment decisions[67]. Several questions reflected the expectation that patients should routinely be provided with information pertaining to side-effects and immediate and long term impacts of cancer and their respective treatment options[68]. This is also echoed in the UK's National Cancer Strategy[69-71] published by an independent taskforce, clearly outlining the intention to address patients' reports of deficiencies in the information they were currently given regarding their treatment options in their five year plan. The American Society of Clinical Oncology has a PRO committee that is developing and testing PRO measures, which, in the future, may be used to assess quality within ASCO's Quality Oncology Practice Initiative[72].These signal not only a shift in policy but the development of a structure of accountability that ensures changes in practice are maintained.

Despite indications of the continuing utility of PROs in cancer, particularly within some specific cancer sites[73-76], there are some limitations pertaining to the measures themselves and their use in practice. These include their content validity[77] and sensitivity to domains relevant to patients and those living with and beyond cancer[78]; and potential barriers to their delivery and implementation such as length and complexity of measures or burden on well and unwell patients[79].

6. Conclusion

PROs are commonly used in cancer research studies and are being increasingly used in routine practice. Health policy-makers are drawing upon PRO data and the generation of PRO data appears to be integrated more into routine practice than ever before, with resource allocation and clinical decision-making being informed by these data.

While the quality of the data collected in cancer clinical trials may limit their use in informing clinical care and health policy, the widespread adoption of guidelines by journals, funders, and research organisations may provide the solution by holding investigators to high standards of practice. To ensure research findings reach the necessary audiences, new avenues for dissemination must be identified so clinicians and patients are able harness PRO research and incorporate it into their decision-making and practice.

In the context of supporting those living with and beyond cancer, PRO data may be used in addition to other indicators, such as biomarkers and clinical tests, to signify the use of particular treatment strategies in the handling of survivorship-related disease. PRO data collected from these individuals also provides opportunity to use this information to indicate when further investigation is required through other clinical means.

7. Expert commentary

As has been identified throughout this paper, a key priority in the field of PROs is to uphold and promote best practice principles in the collection and reporting of PRO data so that the patients' perspective remains central to clinical trial outcomes and routine care. This is particularly important given the rapid evolution in the treatment of cancer and provision of care to those living with and beyond cancer.

Relevance and use of PROMs requires that they retain face, construct, and content validity, as well as reliability, and sensitivity to change in patients' conditions[17, 80-83], making their continuous revision an ongoing exercise. Ensuring their effective delivery and implementation with minimal burden upon participants is vital[84]. Failure to do these would significantly undermine their utility in clinical trials and routine care settings, however the field has issued guidance to uphold good practice and promote effective use of PROMs[85-87]. The SPIRIT-PRO extension[40] aims to facilitate the collection of high-quality data that may inform patient-centred care by improving the PRO-related content in clinical trial protocols. These accompany the CONSORT-PRO extension[42], recommended for use in addition to standard CONSORT guidelines[88] to enable robust interpretation of PRO findings from RCTs and inform patient care. However, the extent to which these may have an impact on practice is determined by their adoption and endorsement by key stakeholders.

Meanwhile, evidence continues to emerge emphasising the continued role of PROs in the early assessment of psychosocial factors following cancer. The CREW Cohort Study[89] demonstrated how

psychosocial factors prior to surgery predict recovery trajectories following cancer treatment independent of treatment or disease characteristics. These findings signify implications for the management of cancer and demonstrate how PROs may be used to identify support needs during the treatment phase, changing patient pathways, and improve recovery as a result.

8. Five-year view

Increasing levels of survival following cancer is resulting in greater numbers of cancer survivors, including those with incurable but treatable cancers, and greater diversity of experience among those individuals with specific and complex sets of needs. Managing and promoting the wellbeing of these groups requires an approach that incorporates consideration for their quality of life[90]. For those involved in cancer research, this requires a shift in focus from commonly used outcomes such as overall survival, to outcomes that encompass the quality of survival. This is integral to the generation of an evidence base that may underpin future policy, practice, and treatment choices[91]. Data generating activities include initiatives including the global TrueNTH registry[92] whereby care provided to men with localised prostate cancer may be monitored through the collection of PROs alongside clinical data. Five years from now, the cancer survival trend will necessitate continued research to better understand and support the changing needs of survivors.

9. Key issues

- Further research is needed on the impact that cancer and its treatment has on the everyday lives of people living with and beyond cancer.
- Patients must have access to information relating to quality of life and survival, with which they can make more informed decisions about their care. However, there are few established outlets for the publication of PRO data which are easily accessible by cancer patients and clinical groups.
- PROs may be used in addition to clinical data to supplement clinical findings and attain a holistic understanding of patients' status. However, research suggests that the collection of PROs from participants is often inconsistent, creating a potential source of bias in the resulting data.
- PROs are being increasingly used as a component of routine practice. Their use has been associated with richer discussions of patient outcomes, improved symptom control, increased supportive care responses, patient satisfaction and wellbeing.
- Continued efforts are required to ensure that PROMs remain sensitive to the needs of patients and barriers to their delivery and implementation are minimised.

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