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Use of patient reported outcomes to measure symptoms and health related quality of life in the clinic

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Abstract

There is increasing interest in the use of patient reported outcomes (PROs) in routine practice in cancer care to measure symptoms and health related quality of life (HRQOL). PROs are designed to capture the patient's perspective of their care and treatment, and complement the traditional clinical outcomes of survival and toxicity assessment. Integrating routine collection and feedback of PROs has been found to improve care for patients on both an individual level, through improved communication and management of symptoms, and at an organizational level, by enabling aggregation of data to compare performance. This article reviews the benefits and challenges of introducing patient-reported assessments into routine clinical practice. Methods for choosing a questionnaire; collection and presentation of results; timing and frequency of administration as well as clinician training methods to aid the ability of clinicians to integrate the use of PROs into their own practice are described. Electronic PRO capture and integration with electronic health records seems to provide the most effective method for seamless integration into existing patient care pathways. Case studies from our own practice illustrate the issues raised. Electronic methods enabling immediate collection, scoring and interpretation of the data, as well as real-time data capture, email alert systems and individualized, online self-management advice may enable severe symptoms to be managed in a more timely manner. Evaluation methods are described to establish the effectiveness of the PRO intervention. Engaging stakeholders throughout the process of initial consultation and development, during delivery and evaluation is key to success. Future work needs to focus on the effectiveness of PROs in

longer-term follow up of patients in routine care and the relationship between the PRO severity grading and clinician severity grading using the Common Terminology Criteria of Adverse Events (CTCAE).

Introduction

Clinician reporting of patient's symptoms as a grade of toxicity has been the usual source of adverse event (AE) reporting in clinical trials and routine practice in all areas of medicine. However, over the past decade in cancer clinical trials the research community has shifted to include patient reported outcomes (PROs), as a standard data source to capture patient's subjective experience, usually as a secondary endpoint(1). PROs are standardised, validated questionnaires that are completed by patients and measure a broad range of health-related constructs including symptom assessment, evaluation of function and health-related quality of life (HRQOL)(2). It is increasingly recognised that inclusion of validated PRO assessments within clinical trials can provide important data for clinicians to inform treatment decision-making. Within the clinical trial literature there are numerous examples of where clinical decision-making has been influenced by the outcomes of the PRO assessment(3).

In addition to their use in clinical trials, PROs have also been found to provide patient benefits when used in routine care. PROs may be used flexibly to achieve multiple objectives in clinical practice depending on the goal of the intervention(4). At an individual level, PRO data may be collected as a one off

screening for AE or used as a method of monitoring changes in problems over time (4). Feeding back the PRO information in a structured format to the clinician can promote patient-centred care by highlighting an individual's concerns(5). Improvements in symptom or function monitoring, and patient-physician communication have been found(5-7). On a systemic level, individual's PRO information may be collated and used within or across organizations to look at the impact of treatment on cohorts of patients and as a performance measure to assess quality of care(8). Although the research evidence for the benefits of using PROs in clinical practice is increasing, some results are conflicting and wider implementation has not been achieved.

This article aims to review (1) the benefits of introducing patient-reported assessments into routine clinical practice and consider the impact at both an individual and a systemic level; (2) describe the challenges associated with implementation including: a) choosing a questionnaire; b) methods for collection and presentation of results, including use of electronic methods; c) clinician training methods to improve integration; and d) discuss the frequency and timing of administration; (3) describe case studies from our own practice to illustrate the issues raised; (4) explore different methods to evaluate the effectiveness of the PRO intervention. The article will conclude with descriptions of future developments in this area of research in cancer care.

Benefits of integrating PROs to measure symptoms and HRQOL in routine practice

Cancer treatment, including gynecologic oncology treatments, increasingly involves multiple agents and multiple treatment modalities. The combination of treatments aims to improve cancer outcomes without significantly increasing the toxicity experienced, however all cancer treatments will at some point in their delivery impact on a patients' quality of life. The treatment modalities commonly used– surgery, radiotherapy and systemic therapy - are often managed by a different set of clinicians, who may or may not reside within the same organization. This organizational complexity, in addition to the multiple different PRO instruments available, creates an almost infinite range of possibilities of how to integrate PRO data collection in an organization. However, widespread, systematic use of PRO data collection across specialities and organizations has the potential to hugely impact on the quality of information regarding acute and long-term AE despite organizational challenges.

The most extensive literature has been on the use of PRO assessments in the monitoring of AE and HRQOL associated with systemic treatments. Measuring the acute AE associated with systemic treatments such as chemotherapy provides the opportunity for regular collection of PRO data to inform dose reductions, treatment modification, supportive care and educational support based on symptom and QOL assessment(9). In radiotherapy and surgery, whilst patients experience acute side effects or complications from treatment, other AE may not manifest until months or years later and cause greater problems(10). The integration of prospectively

collected PROs into routine practice may provide consistency in long-term follow up between different clinicians and organizations for the long-term AE of radiotherapy and surgery, as well as chronic chemotherapy-induced symptoms such as fatigue and neuropathy. By using standardised and validated PRO tools and baseline assessments clinically important differences over time may be evaluated. This may allow empirical identification of AE in patients who may benefit from an active intervention in the short and long term following treatment and allow cohort assessments of PRO data in association with treatment details to evaluate performance to improve future treatments(11, 12).

The inclusion of symptom and HRQOL PROs into routine care may offer additional benefits to the collection of clinician AE data. Although the use of the Common Terminology Criteria for Adverse Events (CTCAE) is well established for the collection of clinician-reported AE data with systemic treatments, it is only since its revision in 2003, that items for radiotherapy and surgery have been incorporated(13). The CTCAE has been accepted as the gold standard for AE reporting in cancer clinical trials(14) and is often used in routine care in oncology to guide treatment decisions despite its development specifically for use in clinical trials(15). However, despite widespread availability of clinician-reported tools, such as the CTCAE, research into symptom reporting in both clinical practice and trials has found systematic under-reporting of symptoms by clinicians when compared to patients(16-18). When a clinician reports on a subjective symptom this requires clinical

interpretation and then requires the clinician to decide on the severity of the problem. This may lead to poor inter-rater reliability and well as incomplete reporting of symptoms(15, 17). Other research has highlighted that most clinicians screen for side effects through history-taking rather than using formal tools(19). This inevitably leads to heterogeneity in the methods of reporting on the presence or absence of an AE. Clinical audit in our organization has shown that this variability is dependent on the organization of the clinic and training of clinicians. Documentation of symptoms was via dictation following consultation but clinicians rarely referred to grades of symptom severity(20). This lack of systematic data collection through clinician-reporting in routine practice has been highlighted as a barrier to future treatment optimization(11, 21).

The benefits of using PROs in clinical practice may be broadly split into individual benefits, to both the patient and clinician, and systemic benefits, where the impact of treatments may be audited within and across organizations to assess performance and quality of care(8, 22).

Benefits to patients and clinicians at an individual level:

The main focus of research into PRO implementation in clinical practice has been the improvement of patient care at an individual level. It was hypothesised that by asking patients to routinely complete questionnaires about their symptoms and level of functioning in a broad range of health

constructs that this may improve the ability of patients to communicate concerns in that can inform the clinical consultation. By providing patients with the language to communicate and by prompting patients about the potential side effects they may experience, the process aims to engage patients more actively in their own care(9). Improvements in communication between physician and patient are the most commonly reported benefit of routine PRO collection. This was seen in 70% of 47 studies reviewed by Hayward et al.(23).

Table 1 provides an overview of randomized controlled trials (RCTs) in oncology evaluating improvements in individual patient care(5, 24-29). The RCTs show consistently that using PROs in daily oncology practice leads to improvements in patient-doctor communication with increased discussion of symptom and HRQOL issues. Some studies have also found reductions in distress and improvements in HRQOL through the use of PROs. However, the RCTs have consistently found no clear impact on decision-making or satisfaction with care. The results reflect the challenges with conducting RCTs of complex interventions and many of the findings are explored through secondary analyses with some conflicting results.

Provision of PRO results to the clinician prior to consultation appears to be a key part of integrating PRO data collection in routine practice. Our research group conducted a RCT to evaluate the importance of this feedback process. In two of the trial arms patients receiving chemotherapy were asked to self-report on HRQOL (using the EORTC QLQ-C30(30) and Hospital Anxiety and

Depression Scale (HADS)(31)) via touch screen computers before each clinic appointments for six months. One group of these patients had their responses fed back to their clinician prior to consultation (intervention group), the other (attention-control) group simply completed the questionnaires. The third control arm did not complete a questionnaire. The trial demonstrated that the process of shared communication with clinicians (in the intervention group) resulted in improved physician-patient communication, which was significant enough to be reported by patients(5, 32). The study also highlighted that patients demonstrated a clinically meaningful improvement in their HRQOL in the intervention arm when compared to the control arm and this was associated with explicit use of the HRQOL data in the consultation. Importantly, although the intervention increased the discussion of non-specific and chronic symptoms, this did not significantly increase the duration of the consultation(5).

Despite high-level agreement for many AE reported by patients and clinicians, research has been able to demonstrate that using PROs in clinical practice can provide data on a wider range of toxicities, including a greater number of mild AE(16, 33). Patients report on symptoms earlier and more frequently than clinicians, and clinicians were found to down grade or miss symptoms such as pain, dyspnea and fatigue(16, 17, 33, 34). Higher-level agreement is seen with symptoms such as diarrhea and vomiting, which may more easily be quantified(16).

Interestingly incorporating PRO assessment into routine care does not seem to improve patient's satisfaction with their care in oncology(9, 23, 35). Satisfaction may be more related to the overall experience of their treatment and influenced by a "ceiling effect" of high satisfaction typical for cancer patients. However, patient engagement and empowerment through improved communication, promotion of collaborative and informed decision-making, and improved education has been well documented(22). Patients report that the inclusion of PROs in their clinical follow up made them feel 'more in control of their care' ((page 3559)(9)). As many treatment decisions are based on a complex balance between the costs and benefits of treatment the inclusion of PROs to facilitate this process may help patients and clinicians understand the different priorities in a patient care(36).

The impact of PROs on management decisions is more complex to determine with conflicting conclusions found in review articles. Earlier reviews of the medical literature concluded that although clinicians report on the importance of HRQOL in their clinical decision-making, in reality the majority of their treatment decisions were based on biomedical factors(37). A more recent review across all healthcare settings of interventions designed to enhance patient participation in the consultation process (including PROs) (23) reported that 56% of 32 reviewed studies reported a change in provider diagnosis and/or management of patient conditions. A systematic review of qualitative literature found clinicians conflicted on the positive impact the use of PROs in clinical practice had on care processes and outcomes(22). Improvements in communication, patient education, patient confidence and

promotion of joint decision-making were described. But some professionals were concerned the PRO data provided them with no additional information and had the capacity to narrow the conversation potentially diverting discussion from important aspects of care(22). These conflicting findings highlight the challenges of identifying changes to decision-making, and the importance of collaboration with clinicians when developing PRO interventions so the process is transparent and the data collected useful in guiding decision-making in individual patient care.

Benefits to patients and clinicians at a systemic level:

The systemic benefits of the integration of PROs into routine care have more recently been evaluated at the organizational level. Although patient mortality has been the traditional outcome measure used to assess quality of care it has been argued that inclusion of measurements of improved health status, along with appropriate risk adjustment for case complexity, may capture important information regarding care quality(38). PROs have been suggested as one method of assessing patient's health status as a key outcome measure of healthcare(38). A number of recent reviews have considered the impact of introducing PRO collection into routine care on the cost effectiveness, overall economic benefits, and evaluation of healthcare quality improvements within and across healthcare providers and individual clinicians(8, 22, 38).

Individual PROs may be aggregated within an organization to assess a cohort of patients who have a particular disease or received a particular treatment to review treatment efficacy. If standardised PROs are used, and as long as case-mix variables are carefully considered, this data may also be used to evaluate across different providers to review the quality of care and assess provider performance(39). Combining PRO data with cancer registry data is feasible and may allow risk adjustment of PROs across organizations, however, it is not clear which variables are important for risk adjustment and further work in this area is needed(12, 40, 41).

Outside of cancer care the UK's National Health Service started the first nationwide routine collection of PRO data before and after elective surgery for hip and knee replacements, and hernia and varicose vein repairs(42).The pilot study established the feasibility of the nationwide project with a cost of approximately $11 per person for postal PRO collection, received positive feedback from stakeholders, and demonstrated high response rates between 80-90%(43). The systemic aims of this venture included measuring provider performance, linking payment to performance, improving referral between primary and secondary care and regulation of safety and quality(8). A recent report established that nationwide PRO data collection was feasible (66% response rate preoperatively and 74% postoperatively) for elective surgical procedures and, when adjusted for case-mix variables, it was possible to calculate quality adjusted life years (QALYs) for individuals, to establish the comparative cost effectiveness and technical efficiency of different

hospitals(44). This approach could be used in oncology to evaluate similar goals.

Another possible systemic benefit to remote PRO data collection could be the potential to re-design follow up care for cancer patients after treatment. The traditional method of regular hospital visits predominates in clinical practice(45, 46). However there is no evidence from prospective studies in gynecological oncology to suggest this method is more effective than other approaches at identifying recurrences earlier or impacting survival and may delay presentation of symptoms(47). Discussion around the cost effectiveness of hospital-led follow up, and concern about the increased anxiety experienced by patients around their hospital appointments, has led to consideration of alternative models including the use of PROs(48, 49). The regular collection and evaluation of PRO data could reduce the intensity of routine clinical follow up and improve the identification of treatment-related toxicity and therefore be considered as an alternative to traditional hospital follow up.

With the Internet accessed by 75% of the US population(50) using a web-based system to measure PROs remotely is attractive and may allow a more consistent method of monitoring late side effects and detection of symptomatic recurrences when patients do not routinely attend the hospital or are followed up by different specialty teams. However, a recent systematic review found there are currently no studies with gynaecological cancer

patients published on this topic so this alternative model of follow up remains untested(51).

Radiation treatment may be used as an example of how integrated PRO collection in routine care may be used in treatment optimization. Improved imaging and computational radiotherapy planning techniques, such as intensity-modulated radiotherapy (IMRT), have enabled more accurate targeting of the tumour or volume at risk. This focussed delivery of radiation to the target volume has enabled clinicians to consider dose escalation to improve cancer outcomes. However, the technique leads to more of the surrounding normal tissue receiving a low dose of radiation than conventional treatments, with an unknown effect on toxicity(11, 52). The toxicity profile has also changed through the increased use of concomitant systemic therapy with radiation treatment(53-55). These approaches are increasingly used in gynaecological cancer patients. Having high quality PRO data could enable institutions to evaluate their short and long-term AE outcomes in combination with information on patient comorbidities, medications known to impact on toxicity severity as well as information on the dose and volume of normal tissues treated with radiation(11, 56, 57). This high quality information could provide evidence for developing safe dose-volume constraints for normal tissues in the future.

Challenges to implementing PRO use in clinical practice

Implementing the integration of PRO assessments into routine care may be considered as a complex intervention. Key components need to be addressed

for the whole intervention to work(58). It is important to establish the effectiveness of an intervention in everyday practice, but this involves understanding the whole range of potential outcomes and how the effect of the intervention varies between patients and clinicians, between specialties, treatments and diseases and within and between organizations(59). This section describes the main components and provides guidance on how to address them.

Which PRO measure to choose?

The hypothesis and outcome of the research need to be established, as the choice of instrument will depend on the overall project aims; for example, symptom monitoring or establishing a screening tool. A number of reviews and websites such as PROQOLID are available to help guide this process (60, 61). Copyright clearance, permissions for use and costs associated with the use of some PRO instruments may also need to be considered.

It is important that all stakeholders involved in the research value the selected measure for the implementation to be a success(61). This may be challenging, particularly if the intervention involves different treatment specialties or organizations. Agreement on one particular instrument may be difficult but inclusion of more items may be burdensome. Some of the barriers to achieving the benefits of PRO interventions may be dispelled through consultation with health professionals and patients who will be involved in the intervention to establish relevant measures and keeping the objectives for PRO data collection transparent at all times(22).

In the clinical setting, the majority of studies have used a combination of a generic and a disease-specific questionnaire. This combination enables assessment of general health domains like physical or social functioning using questionnaires such as EORTC-QLQ-C30 or FACT-G, as well as symptom-specific instruments, which are related to the disease or treatment; for example, for patients with cervical cancer FACT-Cx or EORTC-QLQ-CX24(61). Selection of PROs covering clinically relevant issues that will be discussed at hospital follow up aims to not add additional cognitive demands to the clinicians but instead to act as a guide to support communication and work as a method for systematically recording clinically relevant data for future analysis.

Some instruments are developed to be applicable across diseases and are not cancer-specific, for example, the National Institute of Health's (NIH) Patient-Reported Outcome Measurement Information System (PROMIS)(62). PROMIS aims to provide free access to standardized PRO measures, which have been calibrated and referenced to the US general population(62). The item banks cover both generic (e.g. physical function) and more specific items (e.g. sexual function)(63). PROMIS integrates the use of item response theory (IRT) and computer adaptive testing (CAT) to create individualised questionnaires. IRT is a psychometric method, which statistically models a calibrated score based on an individual's response to a question. The CAT software then uses the calibrated score of the initial question to provide a follow up question that will provide the most information. Collaboration with

Epic (a widely used electronic health records (EHR) system in the US) has led to the integration of PROMIS scored PRO data into EHRs in adult and pediatric settings. Further integrations with EHR software are planned(64). The web-based platform for PROMIS data collection is also available free of charge and an international extension of PROMIS is in development(63).

Methods for collection of PRO data:

For the clinicians to be able to use PRO information effectively at the point of care with a patient, it is important that the data is collected, scored and presented before the consultation in a way that does not interrupt the clinical workflow or create significant cognitive demands on the clinician. Electronic methods, using Internet based questionnaires or touch-screen computers, may be best placed to enable a seamless pathway and integration with patient EHR may further improve the usability of such an approach(12).

Electronic data collection:

Electronic methods for patient reporting have been found to be acceptable to patients and provide better quality data than paper methods(9, 65). For patients without Internet access, the feasibility and acceptability of touch-screen computers/tablets used in waiting rooms has been established, with compliance rates from 75-85%(9, 66-69). Patients are also willing to complete PRO assessments using home Internet (9) or mobile devices (70).

Using weekly email reminders to patients in one study led to an 83% monthly and a 62% weekly compliance rate with patients on chemotherapy over a

mean eight month period(71). The high responses rates provide positive evidence for the use of electronic PRO data collection in routine practice.

The use of real-time automated email alerts to clinicians to flag patients' experiencing serious symptoms was also evaluated in this study(71). Patients who reported a high-grade toxicity or a significant change in scores had an email alert triggered to their responsible clinician in real-time. This may enable capture of AE data impacting on patients during their time at home, which they may have forgotten by the time they return for their next consultation(72). This information may be used to contribute to more accurate treatment decision-making and, if captured in real-time, may enable more prompt assessment and support of any serious symptoms(9).

Presentation of results:

For long-term sustainability of PRO use in clinical practice research suggests that focussing on ease of use and clinically relevant issues are key(73). As EHRs are increasingly used in clinical practice ideally electronically collected PRO results should be integrated into them(12, 61), although in paper-based clinics, the PRO results should be presented in hard copy. The research in this area is in its infancy with significant variability in the approaches used to achieve EHR integration in published research(74). One of the main technical challenges to integration with EHR is ensuring patient confidentiality is not breached. Jensen et al (74) provides an excellent overview of the different electronic PRO systems currently in use in clinical practice. Other issues lie in

436 the fact there are no standard methods for how best to present the PRO data.
437 This review will focus on the latter clinical challenge.
438
439 The PRO data collected needs to make sense to the viewing clinician and
440 therefore the formatting of the results needs to be considered(75). Graphical
441 styles have been found to be helpful and are possible to deliver with electronic
442 collection and scoring of patient responses(61, 76). Tabular and graphical
443 formats enable changes over time to be clearly seen in relation to the
444 completion date of the questionnaire. The alternative is to present the numeric
445 scores of each item or grouped items (see figures 2-3 for examples). Ideally
446 the presented PRO data should provide information about the clinical
447 importance of an individual's scores or on what constitutes a clinically
448 important change to aid decision-making(77). Data on interpretation of scores
449 and normative data is available for some questionnaires(78), however for
450 many questionnaires this information is not available. Initially, through
451 consultation with clinical experts, pragmatic decisions about severity of item
452 responses in relation to clinical need can be made. These cut off scores can
453 be used as a guide to aid interpretation of results and then through more
454 extensive use and analysis of the items in routine practice more evidence-
455 based clinical cut-offs can be established.
456
457 *Frequency and timing of administration:*
458 The frequency and timing of administration of the PRO data collection must
459 also be considered, weighing up the potential burden versus the usefulness of
460 PRO completion by patients and evaluation by clinicians. Although frequent

data collection could provide a more detailed picture of a patient's experience this may result in more variable scoring, which could be challenging to interpret(61). If completion of the PRO assessment becomes burdensome to patients, this may also lead to significant missing data. Whilst incomplete data sets are less of a concern when considering use in practice as compared to clinical trials, for the PRO data to be meaningful for the purposes of internal audit it is important that sufficient data is collected.

If collecting data on AE, for example, each treatment area may vary in the timing and frequency of administration required. Systemic treatments are often episodic, with the majority of side effects occurring acutely, therefore weekly or 'at any time' availability of web-based questionnaires may be beneficial to record PRO information intensely. For surgery, it may be best for the first PRO assessment after baseline to happen months following surgery after patients have fully recovered(12). In radiation treatments, patients require support for acute AE during treatment and in the few weeks after treatment more intensely. However, late toxicity may have an insidious onset and may not manifest until many months or years later(10). For AE developing months after treatment, association of the PRO data collection with follow up consultations may enable further discussion and support of any issues(12).

Training of clinicians:

Training can aid the ability of clinicians to integrate the use of PROs into their own practice. Although clinicians more readily interpret and use symptom

scores in their consultation, they rarely discuss even serious functional problems(79). Training can help clinicians to interpret the meaning of PRO results and to develop effective approaches to respond to issues raised. One method may be through explicit reference to the PRO data in the consultation, creating an opportunity for patients to elaborate in further discussion about their problems(80). When used effectively the data may be used as an ice-breaker to open up conversations on challenging topics such as sexual functioning(24). Clinicians may focus on areas where interventions may change the outcome rather than on problems, such as a decline in cognitive functioning or fatigue, for which there is inadequate evidence for how to avoid the problem or a lack of treatment interventions and may avoid problems they consider they are not personally able to help with(24, 80, 81). However, within a multidisciplinary team setting it may be possible to collaborate with other members using each other's different areas of expertise to enable patients to receive support for all issues raised(82). The training program may enable a process of consultation with multidisciplinary team members to develop management guidelines and signposting of available services for difficult symptoms so clinicians are not concerned about raising challenging issues(80).

A case study in gynaecological oncology:

In response to these different issues, our research group has developed a Internet-based questionnaire collection system, QTool(40). This system allows patients to self-report on symptoms during and after treatment at home or in clinic and has been integrated with Patient Pathway Manager (PPM),

Leeds and Yorkshire Cancer Network's EHR system(83) (see figure 1). Data is collected in protected databases and can be analysed for the purposes of audit or research. PRO assessments are analysed and scored automatically and may be viewed in either a graphical or tabular format. Figures 2-3 describes an example of a patient treated with chemoradiotherapy followed by brachytherapy for cervical cancer.

Abnormal results are highlighted in the results table in red, as used in the presentation of blood results out of normal range, and line graphs are used to see significant changes over time at a glance. High-grade toxicity results are highlighted in real-time by the use of email alerts to attending clinicians to enable prompt assessment. In addition, patients are immediately provided with individualised online self-management advise for mild to moderate severity symptoms based on their responses(83). The system is being evaluated for patient and staff acceptability and over the past six months 175 patients (including gynecological cancer patients) have completed the questionnaire, either as a single assessment or as part of a longitudinal study. Early feedback from clinicians has been positive with improvements in structuring consultations described and easing the process of bringing up more challenging topics such as sexual dysfunction, without impacting on the clinic flow. Patient feedback on the alerts and self-management advice has been positive. One patient exemplifying the general feedback received following the feasibility pilot study, described the process as 'a safety net for you and gives you the help to keep going on through your treatment'.

Evaluating the effectiveness of PRO interventions:

As a complex intervention, the evaluation of PRO effectiveness in clinical practice is challenging. The aim of evaluation is to measure a process of social change, which involves a complex, non-linear and interpersonal system sensitive to multiple influences, such as different environments, leadership, and the details of the intervention(84). Traditional methods for evaluation such as RCTs may not capture how and why the PRO intervention works and other study designs such as quasi-experimental, observational or service development and evaluation models may be better suited(61, 84). Whilst RCTs provide a powerful method to explore individual components of clinical practice by minimising bias this may remove what is effective about the organizational context or mechanism used for implementation. The challenges of the RCT approach may be seen in the conflicting results of the RCTs described in Table 1. In the setting of complex intervention evaluation it is recommended a qualitative assessment is incorporated into RCTs to establish the how, why and what works about the intervention(61, 84).

Quality improvement methods can be recommended as they provide evidence of effectiveness, may be cheaper to run and many institutions have programs in place to support implementation research(61). These methods aim to make small, incremental change and to evaluate and modify based on outcomes along the way, such as in the Plan-Study-Do-Act (PDSA) cycles. These methods are uncontrolled but employ qualitative assessment to observe how the PRO is used by clinicians and patients and how it is integrated into the workflow. This type of evaluation enables consideration as to how the change

has occurred and what aspects are generalizable to other contexts by establishing the local conditions that have led to successful outcomes(84). In the initial stages, this quality improvement approach may also be used as a process of consultation to engage stakeholders and improve the effectiveness and value of the PRO intervention.

Future work into PRO use in clinical practice

Future work needs to focus on the effectiveness of PROs in longer-term follow up. Most patients treated curatively for gynaecological cancer will be followed up for five years for monitoring of disease recurrence. But so far research into PROs has only followed patients up outside of clinical trials for eight months(71). The use of Internet-based PROs in longer-term follow up may enable clinicians to re-design follow-up care. For example, assigning remote regular PROs completion and monitoring of results, may potentially enable follow up through telephone consultations or email if patients report no significant problems(51).

Although in clinical trials research PROs are often used as a surrogate for late AE reporting the relationship between the PRO severity grading and clinician severity grading using the CTCAE is not yet established. For symptom based PROs to be accepted as a valid addition to clinician-reporting of symptomatic AE this relationship needs to be made clearer. Clinical consensus has been used in one meta-analysis of clinical trials, as a pragmatic method to compare the grading scales of two reporting systems(34). The scores for six symptom items in the EORTC-QLQ C30 were matched to a grade or grades in the

CTCAE (version 2) (e.g. EORTC score 2 (‘a little’ response) equivalent to CTCAE score 1 (mild); EORTC score 4 (‘very much’) equivalent to CTCAE scores of 3 and 4 (severe/life threatening)). However, this approach assumes the homogeneity of both systems in terms of what separates a grade 1 AE from a grade 2 or 3 and whether this is of clinical significance to the patient. Whilst validated PROs often have had extensive psychometric testing to establish the differences between item scores, the CTCAE has evolved as a clinical tool and has had no formal validation of these issues(85). The National Cancer Institute’s PRO-CTCAE initiative aims to address these issues by mapping the validated PRO-CTCAE items generated back to the CTCAE in all treatment domains to establish clear links(86), however, for other validated PROs in common use there remains a deficiency of knowledge in this area.

Research into PRO integration into clinical practice is continuing to grow and develop. In more recent years the focus has been on the use of health information technology through Internet PRO data collection and real-time integration with EHR. This approach has the potential to improve implementation, aiming to seamlessly integrate the use of PROs into the normal clinical workflow. If used judiciously, integrated PROs have the potential to reduce human workload and provide support and feedback to patients in a timelier manner(22, 87). Engaging stakeholders in the development, implementation and assessment of the PRO intervention is likely to improve the success of the venture, at both an individual level, for patient and clinician, and the systemic effectiveness within and across organizations(22).

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Table 1: Randomized controlled trials (RCTs) in oncology evaluating symptom and HRQOL based PROs in routine practice

AUTHORS	DESCRIPTION OF INTERVENTION PROCESS AND OUTCOMES	POSITIVE OUTCOMES	NO IMPACT OR N/A	COMMENTS
McLachlan 2001 (27)	Patients (N=450) **completed self-reported cancer needs (CNQ), HRQOL (EORTC-QLQ C30) and psychosocial information (BDI) using touch screen computers.** (1) **Intervention:** 2/3 patients randomized to have PRO information fed back to clinical team with a coordinating nurse present to implement the referral pathway proposed following consultation or (2) **Control:** usual care. **Primary outcome:** Change from baseline psychological and information needs (from CNQ). **Secondary outcomes:** Other domains of CNQ, QOL, psychosocial functioning at 2 and 6 months and satisfaction with care (non-validated questionnaire) at 6 months	Patients who moderate to severe depression had significant benefit from intervention at 6months (p=0.001; secondary analysis). Patients endorsed touch screen computers.	No significant difference in primary and secondary outcomes.	No clinician training provided on the use of the PRO data. Patient satisfaction with care was high for all groups.
Detmar 2002 (26)	**Routine HRQOL (EORTC-QLQ C30) screening (graphical paper report):** Prospective randomized cross over trial. Patients (N=214) receiving palliative chemotherapy were randomized to (1) **Intervention:** completion of EORTC-QLQ C30 at 3 successive outpatient visits with results fed back to clinical team (2) **Control:** usual care. Clinicians switched to alternate arm of study mid way through study recruitment. **Outcomes:** Communication about HRQOL (content analysis of audio-recorded consultations); HRQOL, Satisfaction with care, patient management, physician awareness (COOP/WONCA),	Communication scores significantly improved in intervention arm (4.5 vs 3.7; p=0.01 effect size = 0.38). More patients in intervention group received counselling on how to manage health problems (23% vs 16%l; p=0.05)	No differences in physicians' awareness (COOP/WONCA); Referral patterns or medication/test management; HRQOL scores; duration of consultation. Satisfaction with care was high in all groups.	All physicians and 87% of patients believed the intervention facilitated communication and expressed interest for continued use of intervention.
Velikova 2004 (5)	**Routine HRQOL (EORTC-QLQ C30) and HADS assessment on touch screens +/- graphical paper feedback:** N=286 patients randomized to (1) **Intervention**: completion of PRO measures with feedback; (2) **Attention-control**: completion of PRO measures no feedback; (3) **Control:** usual care for 3 consultations (over 6 months) **Primary outcomes:** HRQOL over time (FACT-G); physician-patient communication and clinical management (content analysis of audio-recorded consultations).	Improved HRQOL in intervention and attention-control vs control (p=0.006; SE = 2.84) and p=0.01). A larger proportion of patients in intervention arm had clinically meaningful improvement in HRQOL (NNT 4.2). Increased discussion of HRQOL issues in intervention arm (p=0.03).	No significant impact of intervention on patient management	Trial not primarily designed to look for difference between attention-control and control group.
Rosenbloom 2007 (28)	**Routine HRQOL assessment (paper) followed by nurse-led interview.** N=213 patients on chemotherapy randomized to (1) **Intervention:** HRQOL (FACT-G) completion followed by structured research nurse led interview fed back to treating nurse; (2) **Assessment control:** HRQOL with report fed back to treating nurse; (3) **Control:** usual care over 4 consultations (over 6 months). **Primary outcome:** FLIC; Brief-POMS-17; PSQ-III; clinical treatment changes.		No significant differences between groups in HRQOL (FLIC), satisfaction (PSQ-III) or clinical treatment changes over time.	High QOL/PSQ scores reported at baseline (possible ceiling effect seen). Sensitivity of outcome measures questioned by authors.

AUTHORS	DESCRIPTION OF INTERVENTION PROCESS AND OUTCOMES	POSITIVE OUTCOMES	NO IMPACT OR N/A	COMMENTS
Carlson 2010 (25)	**Routine distress screening using hand held tablet:** Patients with lung (N= 549) and breast cancer (N=585) were randomized to (1) **Minimal screening -** Distress thermometer (DT) assessment plus usual care; (2) **Full screening -** DT, problem checklist, psychological screen for cancer (PSSCAN) for anxiety and depression; report provided to patient and EMR; (3) **Triage -** As for (2) plus option of personalized phone call to access referral services. **Primary outcome:** Distress at 3 months measured using DT. **Secondary outcome:** anxiety and depression measured using PSSCAN	**Triage** group **significantly lower distress** at 3 months than **minimal screening** group (p=0.031)	Intervention had no impact on anxiety or depression measured	
Berry 2011 (24)	**Routine electronic symptoms and QOL (ESRA-C):** Patient with cancer diagnosis (N=660) randomized to (1) **Intervention:** ESRA-C completed on touch screens in clinic and graphical summary presented to clinical team; (2) **Control:** ESRA-C with no summary provided. **Primary outcome:** Communication of symptoms and QOL above predetermined threshold highlighted on summary report. **Secondary outcome:** duration of clinic visit and clinician evaluation of intervention.	29% increase in discussion of symptoms and QOL scored over predetermined threshold in intervention group (odds ratio 1.29; 95% CI 1.1 to 1.6). Greater discussion of sexual items (6.8% vs 2.4%) initiated by clinician.	No impact of intervention on duration of visit.	Clinicians reported the intervention as useful for guiding the interview and identifying problem issues.
Berry 2014 (29)	**Routine electronic ESRA-C assessment in clinic or internet based with self-care education and coaching on symptom feedback to clinicians.** Patients with cancer diagnosis (N=752) randomized to (1) **Intervention:** ESRA-C completed either using internet at home or in clinic. Self-care education and coaching provided to patients in real time and result summary of ESRA-C provided to clinicians. (2) **Control:** Completed ESRA-C and result summary provided to clinicians. Follow up 3-4 months **Primary outcome:** Symptom distress (SDS-15)	Lower symptom distress in intervention arm (SD-15 score reduced by estimated 1.21 (95% CI, 0.23 to 2.20; p=0.02).	Intervention effect was significant for older patients (p=0.01) but not younger (<50years) patients (p=0.2)	Benefit of the intervention greatest in patients >50 years

Key: CNQ: Cancer Needs Questionnaire; HRQOL: Health related quality of life; EORTC- QLQ C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; BDI – Beck Depression Inventory short form; COOP/WONCA: Dartmouth primary care cooperative information functional assessment and World organisation project of National colleges and academics; HADS: Hospital Anxiety and Depression scale; PRO: patient reported outcome; FACT – Functional Assessment of Cancer Therapy (General questionnaire); FLIC: Functional living index-cancer (QLQ); Brief POMS-17: Brief profile of mood states; PSQ-III: Medical outcomes study patent satisfaction questionnaire-III; DT: distress thermometer; PSSCAN: Psychological screen for cancer part C; EMR: electronic medical records; SDS-15 (Symptom distress scale-15)