Qualitative research in evidence-based medicine: Improving decision-making and participation in randomized controlled trials of cancer treatments

Suzanne Audrey  School of Social and Community Medicine, University of Bristol, Bristol, UK

Abstract
Background: Since the 1990s there has been increasing emphasis on ‘evidence-based medicine’. The randomized controlled trial is widely regarded as the ‘gold-standard’ study design for evaluating interventions. However, placing too strong an emphasis on a phase III trial, to the neglect of earlier development and piloting work, may result in weaker interventions that are more difficult to evaluate and less likely to be implemented.

Aim: To illustrate the benefits and outcomes of qualitative research at the early stages of the research continuum.

Setting/Participants: Two cancer studies are evaluated in which the best treatment option is uncertain: ASPECTS (A Study of Patients Experiences of Treatments) and ProtecT (Prostate Testing for Cancer and Treatment).

Design: To examine decision-making in relation to palliative chemotherapy for advanced cancer, ASPECTS was a qualitative study involving non-participant observation and recording of oncology consultations. During the ProtecT feasibility study, recruitment interviews were routinely audiotaped and in-depth interviews conducted with men to explore their understanding of treatment options and randomization to trial arms.

Results: ASPECTS identified that insufficient information was given to patients about the survival benefits of palliative chemotherapy with implications for informed consent. ProtecT illustrated the effective use of qualitative research methods to resolve recruitment and randomization problems for a randomized controlled trial.

Conclusions: These studies illustrate the value of qualitative research, particularly during the earlier phases of the research continuum. Such research may generate hypotheses, strengthen the development and implementation of interventions and enhance their evaluation: all of which are essential to evidence-based medicine.

Keywords
Cancer, complex interventions, decision-making, evidence-based medicine, palliative chemotherapy, patient recruitment, qualitative research, randomized controlled trials

Introduction
Since the 1990s there has been increasing emphasis on ‘evidence-based medicine’.1 The term itself is debated but has been defined as ‘the judicious integration of best research evidence with the patient’s values to make decisions about medical care’2 and ‘the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients’ by ‘integrating individual clinical expertise with the best available external clinical evidence from systematic research’.3 The aim is to assist clinicians and healthcare professionals in developing methods of disease prevention, making proper diagnoses, choosing the best treatment plans, and developing appropriate guidelines that can be used to improve treatment, measure performance and identify areas for further study and improvement.2

The randomized controlled trial (RCT) is a powerful tool for evidence-based medicine and is widely regarded
by the medical profession as the ‘gold-standard’ study design for the evaluation of medications and procedures to improve health. In particular, the random allocation of participants to the intervention and control arms reduces bias and provides the most rigorous way of determining whether a cause–effect relationship exists.\(^4\)\(^5\) Although prominence is given to statistical analyses in relation to primary outcomes, there has been increasing recognition of the role qualitative research can play in generating hypotheses, the development and implementation of trials, the interpretation of results, and the wider application of successful interventions. With its emphasis on meaning, context and process, qualitative research can expand our understanding of ‘what works’ to include ‘for whom’ and ‘in what circumstances’.\(^6\) Appropriately designed and executed qualitative research can be invaluable in ‘reaching the parts other methods cannot reach’.\(^7\)

Because health issues tend to be multi-dimensional and multi-disciplinary, there are strong arguments for developing research that draws upon, and integrates, a wide spectrum of methodologies.\(^8\) Nevertheless, published studies of qualitative methods within RCTs are relatively rare.\(^9\) This is particularly disconcerting in trials of complex interventions where a number of components are important for the functioning of the intervention and one specific effective ‘ingredient’ is difficult to identify.\(^10\)

The term ‘best’ implies a hierarchy of evidence\(^11\) and the focus continues to be placed on RCTs. Attempts have also been made to grade and critically appraise qualitative studies\(^12\)\(^13\) but some clinicians continue to question the rigour and consequent value of qualitative research. Concerns range from a desire for clear guidelines to assess the quality of specific studies\(^14\) to the somewhat hostile rejection of underlying theories.\(^15\) Palliative medicine is an area in which it might be thought that heterogeneity of research methodologies is widely accepted, indeed promoted.\(^16\) Nevertheless, the scope and contribution of qualitative research may be underestimated:

‘My first impression, and I risk a flood of angry rapid responses, is to ask how much more qualitative work we need in this [palliative care] field. While we do publish qualitative studies in the BMJ, we look for works that give particular insights that add significantly to current knowledge and are of importance to our general clinical readership. To use a term from the qualitative literature, I think we may have reached saturation. Qualitative research, in particular, has been very successful in raising awareness of suffering and helped our understanding of the human and personal dimension - there have been very important insights. We now need to look at what we can do about it - measuring the effectiveness of interventions.’

(Domhnall Macauley, Primary care editor, BMJ, 19 April 2011).\(^17\)

Although ‘raising awareness of suffering’ and ‘understanding of the human and personal dimension’ are vital contributions to medical practice, to focus solely on these outcomes of qualitative research is to underestimate the wider contribution to the research process and evidence-based medicine. In 2002 the Medical Research Council (MRC) in the UK issued guidance on the development and evaluation of RCTs for complex interventions\(^10\) which was updated in 2008 to include non-experimental methods.\(^18\) A key message of the guidance, which is increasingly acknowledged by the international research community,\(^19\)\(^20\)\(^21\) is that developing, piloting, evaluating, reporting and implementing a complex intervention is a lengthy process. Each stage of the process is important and placing too strong an emphasis on a phase III trial, to the neglect of earlier development and piloting work, may result in weaker interventions that are more difficult to evaluate and less likely to be implemented.

The ‘continuum of increasing evidence’\(^22\) has several stages: a preclinical, exploratory stage during which relevant theory and design issues are explored; phase I modelling when the key components of an intervention and its evaluation are developed; a phase II feasibility or pilot study when components of the intervention and relevant protocols are tested, and may be modified; a phase III RCT with appropriate statistical power to evaluate effectiveness; and the implementation of an effective intervention in uncontrolled settings over the longer term.

Each of these stages may be enhanced by qualitative research. Initial exploratory work may identify or hone the research question. During phase I and phase II, qualitative findings may contribute to improvements in the design and implementation of an intervention and its evaluation. Similarly, an integral process evaluation during a phase III trial may provide valuable information about context, delivery and receipt of an intervention that may help to explain discrepancies between expected and observed outcomes. If an intervention is adopted for wider implementation, qualitative research may play an important part in service evaluation, assessing the delivery and receipt of an intervention away from the rigours of a trial.

In this paper, the contribution of qualitative studies to the early stages of this continuum of evidence is considered through two cancer studies. Although the examination of patients’ perspectives was critical, the outcomes of the qualitative research related to medical practice and trial design. ASPECTS (A Study of Patients Experiences of TreatmentS)\(^23\) was a
qualitative study that identified reluctance on the part of oncologists to provide information about the survival benefits of palliative chemotherapy, with implications for informed consent to treatment. In the second example, ProtecT (Prostate Testing for Cancer and Treatment), qualitative methods were essential in identifying ways to improve recruitment and ensure that a trial was feasible and acceptable to patients and clinicians. Each study is considered in turn before more general conclusions are drawn.

**ASPECTS: Identifying an issue**

**Purpose**

The purpose of ASPECTS was to explore patients’ experiences of palliative chemotherapy treatments. Despite an increasing body of literature concerned with communication skills and treatment decision making, relatively little was known about this process for patients with advanced cancer. The treatment may involve frequent visits to hospital, considerable disruption to everyday activities and unpleasant side effects. Because survival benefit may be modest, decisions about treatment may be difficult. The broad aims of ASPECTS were, therefore, to use qualitative research methods to describe patients’ experiences of palliative chemotherapy, explore the process surrounding treatment decision-making, and consider ways in which this might be improved. The research protocol was given a favourable opinion by North Somerset Research Ethics Committee.

**Methods**

Forty five patients with advanced cancer were recruited to the study. Three fairly common cancers were chosen: colorectal, non-small-cell lung and pancreatic. The initial oncology consultations, at which treatment options were discussed and often agreed, were recorded and observed. All recordings were fully transcribed and anonymized to protect confidentiality. The transcripts were examined in detail to assess whether information provided at this stage conformed to Department of Health guidance on seeking informed consent to treatment, i.e. whether patients were given ‘enough information to make a decision’ including ‘the benefits they hope will result’ and ‘the chances of getting such benefits’. The dataset for this analysis comprised 37 consultations (three patients were too ill to keep the appointment; two consultations were not recorded; one patient refused to see an oncologist; and the possibility of ‘cure’, judged to be beyond the definition of ‘palliative’ for this analysis, was mentioned during two consultations).

During analysis constant comparison from grounded theory was employed. This entailed reading and re-reading the transcripts to identify themes. The data were electronically coded using ATLAS.ti software. In addition the Framework method of qualitative data management, which entails placing coded data into charts, was used to aid analysis and increase transparency (Table 1).

**Findings**

Data relevant to the stated purpose of treatment and survival benefit revealed consistency in informing patients that a cure was not being sought but considerable variation in the amount of information given about survival benefit. This included: giving specific numerical data (6 of 37 patients); an idea of timescales (5 of 37 patients); vague references (18 of 37); or not being mentioned at all (8 of 37). Examples of each of these are illustrated in Table 1. In the majority of consultations (26/37) the discussion of survival benefit was either vague or non-existent. The topic appeared to be ‘the elephant in the room’: an obviously important issue that people were reluctant to acknowledge or talk about.

Having identified this omission through examining data from the consultations, information available from the National Institute for Health and Clinical Excellence (NICE) was examined. Survival benefit is often the primary outcome measure in clinical research relating to palliative chemotherapy, and data about the survival benefit of relevant palliative chemotherapy drugs was included in NICE guidance for healthcare professionals. However, these data were omitted from the information for the public.

**Implications for practice**

Giving comprehensible and appropriate information about survival benefit is difficult, and the reluctance to inform patients of the limited survival benefit of palliative chemotherapy may be motivated by a desire to protect patients from further bad news. But this reluctance may hamper patients’ ability to make informed decisions about their future treatment. Where chemotherapy is not offered, it may also heighten concerns that valuable lifesaving treatments are being withheld for economic reasons.

The findings from ASPECTS resonated with oncologists attending conferences and workshops at which data from the study were presented. Reluctance to discuss survival benefit was not disputed, but the difficulty of presenting complicated information to distressed patients and their carers was highlighted. This has clear implications for medical practice and
informed consent.\textsuperscript{44} The ASPECTS team concluded that oncologists require support and training in how to communicate relevant information about survival benefit to their patients. In addition, consideration should be given as to whether, and how, NICE should communicate this important information to the public.

Further work is required which may, for example, include the development of a decision-making aid, a training programme for oncologists, or the production of appropriate patient information leaflets. Having moved from the broader exploration of patients’ experiences to a specific issue with implications for practice, future work could include phase I and II development and piloting of an intervention which might then go on to be tested as part of a phase III RCT. In identifying the issue to be addressed, ASPECTS can be seen as the beginning of this process. The next example of qualitative research relates to the feasibility of conducting a trial.

**ProtecT: Ensuring a trial is feasible**

**Purpose**

Although the RCT is the preferred study design for evaluating the effectiveness of medical interventions\textsuperscript{35} recruitment is often lower than anticipated.\textsuperscript{46-48} This problem can be exacerbated for conditions such as prostate cancer where available treatment options are fundamentally different (surgery, radiotherapy or monitoring) and survival benefits are unclear. Despite broad consensus that a trial of available treatments was urgently needed, the ProtecT study team were aware

\begin{table}
\centering
\caption{Section of chart with data on purpose of treatment and survival benefit}
\begin{tabular}{|l|l|l|}
\hline
Decision & Purpose of treatment & Survival benefit & Code \\
\hline
Chemotherapy not offered: patient too unwell & Oncologist: actually it’s not very good at all because it only works for about a third of people who have it, and when it works, it’s transient, it sometimes makes you feel a bit better; sometimes helps the pain, sometimes helps you put on some weight. But that only happens in a third of people that have it, so the majority of people that have it, it doesn’t work. & Oncologist: in the majority of cases it doesn’t work. And even if it does work it can prolong life but only by four weeks. & Numerical \\
Chemotherapy offered and accepted & Oncologist: the aim of treatment is not to cure the cancer but to control it… to shrink the cancer, improve symptoms and quality of life, and to prolong life… there’s a 50:50 chance that we will shrink the tumour and about a 1 in 4 chance that we’ll get some good response and you’ll get real extra benefit from it. & Oncologist: we’re not unfortunately talking about people living years longer, we’re talking about gaining months on the whole. Some lucky people may live some years longer but that’s not the average expectation. & Idea of timescales \\
Chemotherapy offered and accepted & Oncologist: it’s not a cure. It will control the disease and try and keep you as well as possible for as long as possible… It only really works for about 1 in 3 people… it might improve if you've got pain, it might improve your energy levels. & Oncologist: and it might buy you time. & Vague \\
Chemotherapy offered and accepted & Oncologist: we can't get rid of this cancer for you… But we can certainly try and control it and keep on top of it… see what the chemotherapy can do, whether we can shrink it down and to see if we can get any control of, of the cancer. & [Survival benefit not mentioned by patient or oncologist.] & Not discussed \\
\hline
\end{tabular}
\end{table}

*Note: Gender, cancer site, age, and participant IDs removed to protect confidentiality*
of previous difficulties with randomization.\textsuperscript{49–52} In response, they developed a feasibility study to explore and resolve recruitment difficulties.\textsuperscript{24}

**Methods**

During the ProtecT feasibility study, men aged 50–69 were invited to a nurse-led clinic in general practice, where they were given information about testing for prostate-specific antigen (PSA), uncertainties about treatments, and the need for a trial. If the men consented, PSA testing took place and those with abnormal results were invited for further diagnostic tests.\textsuperscript{53} Men diagnosed with localized prostate cancer were randomized in a nested trial of recruitment strategies to see a nurse or urologist who supplied details about available treatments. The need for a trial was explained and the men were asked to consent to randomisation to either a three-arm (surgery, radiotherapy, monitoring) or a two-arm (surgery, radiotherapy) trial. If they refused randomization, a patient-led preference for treatment was agreed.\textsuperscript{54} A multi-centre research ethics committee gave ethical approval for the study.

Initial randomization rates were poor and the following qualitative methods were used to investigate the process of recruitment. Recruitment interviews were routinely audiotaped and in-depth interviews were conducted with men, following receipt of PSA results and diagnosis, to explore their understanding of treatment preferences and their experiences of the study. All interviews were semi-structured, following a checklist of topics to ensure that specific areas were covered while allowing issues that were of importance to individual men to emerge. Audiotapes were fully transcribed and detailed examination of pairs of appointments and follow-up interviews was undertaken to explore the delivery of information by recruiters and its interpretation by patients.

Recommendations for changes to the content and presentation of information were produced and circulated to recruiters. In addition, a training programme for recruiters was developed and delivered. The impact of the recommendations and training was explored by listening to subsequent information appointments. Recruitment, defined as consent to randomization and acceptance of allocation, was calculated regularly.

**Findings**

Four main issues were identified as playing important roles in recruitment: organization of study information; terminology used; presentation of the non-radical arm; and presentation of randomization and clinical equipoise.

Initially, the order in which treatments were presented was: surgery, radiotherapy, and finally monitoring. Early recordings of information appointments and patient interviews showed that the treatments were not presented or interpreted equally. Surgery and radiotherapy were described in detail as aggressive, curative treatments while monitoring was portrayed briefly as a more passive process of watching and waiting. To address this, recruiters were asked to change the order in which the treatments were presented (active monitoring, surgery, and radiotherapy) and to describe their respective advantages and disadvantages in equivalent detail.

Patients may interpret trial and clinical terminology quite differently than intended by practitioners\textsuperscript{55,56} and this was evident in the early stages of ProtecT when, for example, ‘trial’ was sometimes interpreted as ‘try and see’. In this case, recruiters were asked to replace ‘trial’ with ‘study’. The non-radical treatment option caused difficulties for both patients and recruiters. Although this option included regular review, recruiters often used the term ‘watchful waiting’ with the potential for interpretation as ‘no treatment’ or even ‘watch while I die’. This non-radical arm was renamed ‘active monitoring’ with additional emphasis placed on the regular scrutiny of PSA tests and the availability of radical intervention if required or requested. As a result of these changes, recruiting staff were able to express confidence in this treatment option.

Patients and recruiters also had difficulty with randomization. Patients often expressed lay views that cancer should be removed, or came with media information that was biased in favour of radical treatments. Recruiters were asked to encourage patients to express their views and concerns, and to spend time discussing the various treatment options using the ProtecT study information. It was important that recruiters were confident that the men they were recruiting were suitable for all three treatments. In these circumstances, recruiters were able to explain that randomization offered a way of resolving the dilemma of treatment choice. Patients were also informed that if they agreed to randomization, they could take time to consider whether the allocated treatment was acceptable.

As a result of this qualitative work, and the consequent development of different approaches and changes to protocol, recruitment rates increased from 30–40% in May 2000 to 70% by May 2001.\textsuperscript{24}

**Implications for recruitment methods**

Qualitative research methods may be included in studies to help with the interpretation of quantitative results.\textsuperscript{57–59} However, during the ProtecT feasibility study, qualitative research methods were used to
identify and implement changes necessary to maximize recruitment and ensure the effective and efficient conduct of the trial. While it is unethical and counter-productive to employ recruitment methods that coerce patients to participate in trials, this danger may be addressed by providing unambiguous information and allowing potential recruits to make an accurately informed decision about whether to accept randomization. Poor recruitment rates threaten the power and external validity of trials and waste resources. Where available treatments are controversial, randomisation and equipoise may be difficult concepts and place particular demands on both patients and recruiters. This study suggests that qualitative methods should be used during feasibility studies to expose and address issues that may threaten recruitment.60

Conclusion

Although RCTs and statistical analyses are fundamental to evidence-based medicine, there has been increasing recognition of the value of qualitative research methods. Recent MRC guidelines emphasize that developing, piloting, evaluating, reporting and implementing complex interventions is a lengthy process. Focussing too much attention on the definitive phase III trial, to the detriment of developmental and piloting work, can result in weaker interventions, difficulties with evaluation and consequent failure of implementation. Nevertheless, there are continued signs of resistance to the inclusion of qualitative methods as an ‘equal partner’ in the research process. This paper has focused on two studies to illustrate the use of qualitative methods during the earlier stages of the research continuum. Both studies dealt with potentially distressing conditions, requiring rigorous but sensitive investigation.

Qualitative methods can be especially effective when examining the views and experiences of patients, particularly in sensitive areas such as cancer treatments and palliative care. The value of this understanding should not be underestimated. However, it is not appropriate or helpful to suggest that this is the only purpose of qualitative research. The two studies described here illustrate a wider contribution to evidence-based medicine: identifying ways to improve medical practice and improving trial design.

The example of ASPECTS illustrated how a qualitative study with a fairly broad frame of reference identified a specific issue: in this case, where insufficient information was given to patients about the survival benefits of palliative chemotherapy. This finding has implications for informed consent and has identified the potential for an intervention to improve communication skills and decision-making in the field of palliative medicine for advanced cancer. Further along the research continuum, the ProtecT feasibility study used qualitative methods to explore acknowledged difficulties in recruiting to a RCT of prostate cancer treatments. Issues identified by the qualitative research led to changes in the study information, terminology used and presentation of the non-radical arm. In addition, issues of randomization and clinical equipoise were clarified for both patients and recruiters. As a result, recruitment significantly increased and a trial, once thought to be ‘impossible’, became a reality. Lessons learned through the ProtecT study may help to address similar problems encountered in trials of palliative medicine and supportive care.61–64

The studies described here illustrate the value of appropriately designed and executed qualitative research, particularly during the earlier phases of the research continuum. Such research may be invaluable in ‘raising awareness of suffering and helping our understanding of the human and personal dimension’17 of medical practice. But qualitative research may also identify research questions, strengthen the development and implementation of interventions, and enhance their evaluation: all of which are essential to evidence-based medicine.

Acknowledgements

ASPECTS: Professor Rona Campbell, Dr Julian Abel and Professor Jane Blazeby designed the study and wrote the successful research proposal. Dr Stephen Falk provided valuable insight as a practising oncologist. Rona Campbell, Julian Abel, Jane Blazeby, and Stephen Falk were co-authors of the original paper examining the discussion of survival benefit during the ASPECTS consultations.23

The ProtecT study group are: Prasad Bollina, Sue Bonnington, Lynn Bradshaw, James Catto, Debbie Cooper, Michael Davis, Liz Down, Andrew Doble, Alan Doherty, Garrett Durkan, Emma Elliott, David Gillatt, Pippa Herbert, Peter Holding, Joanne Howson, Mandy Jones, Roger Kockelbergh, Howard Kynaston, Athene Lane, Teresa Lennon, Norma Lyons, Hing Leung, Malcolm Mason, Hilary Moody, Philip Powell, Alan Paul, Stephen Prescott, Derek Rosario, Patricia O’Sullivan, Pauline Thompson, and Sarah Tidball. The co-authors of the paper on which the ProtecT section of this paper is based24 were Jenny Donovan, Nicola Mills, Monica Smith, Lucy Brindle, Ann Jacoby, Tim Peters, Stephen Frankel, David Neal, Freddie Hamdy and Paul Little.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. ASPECTS was funded by Cancer Research UK (grant number C17713/A6132). The UK Department of Health funded the ProtecT study through the NIHR Health Technology Assessment programme.
Conflict of interest
The authors declare that there is no conflict of interest.

References
64. Kongsgaard U and Werner M. Evidence-based medicine works best when there is evidence: Challenges in palliative medicine when randomised controlled trials are not possible. J Pain Palliat Care Pharmacother 2009; 23: 48–50.