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The psychosocial responses of patients in cancer clinical trials: are they a barrier to participation?

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Literature Review

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Abstract

Introduction: This paper aims to discuss the psychosocial concomitants with involvement in oncology clinical trials, focusing on barriers that can impact upon participation. It will conclude with some recommendations for strategies to address potential psychosocial barriers with the aim of increasing trial participation rates.

Materials and methods: A literature search was carried out using CINAHL, PubMed and EMCare databases with the following keywords for filtering: psychological distress, clinical trials, participation and oncology. The final selection of papers that met the inclusion criteria for this review was manually subjected to Critical Appraisal Skills Programme tool for relevance.

Results: Thirteen papers were included in the review. The dominant theme within the literature is psychosocial obstacles to oncology clinical trial participation. Five key barriers were identified: anxiety and fear; ethnicity and social background; tensions between scientific objectives and personal motivations to participation; tensions between personal benefits versus altruism; carer perspectives.

Conclusions: The key barriers discussed led to the identification of a set of strategies to help mediate conflicting tensions and motivations of trial enrolment with a view to increasing participation rates. Further prospective research garnering primary data investigating both the psychological and psychosocial factors influencing cancer clinical trial participation for patients needs to be undertaken.

Introduction

Clinical trial results provide the crucial evidence base for establishing the efficacy and safety of novel therapeutic approaches for malignancy before such cancer therapies can be implemented into the clinical setting. Fundamental to cancer clinical research is patient participation. Clinical trials can be carried out more effectively with greater participation, resulting in new treatments being implemented sooner.[1] Moreover, clinical trials may give opportunities for participants to access the newest available therapies.

However, despite over a decade of research into potential barriers, participation to cancer clinical trials remains low. Although the UK, comparatively speaking, has higher rates of clinical trial participation, with 30% of patients reporting that cancer research had been discussed with them,[2] there is a global concern that fewer than 5% of adult patients enrol in clinical trials.[3,4] Poor accrual results in trials remaining open for longer, potentially increasing costs and reducing the opportunity to improve patient outcomes.[5]

The barriers of patient participation in cancer clinical trials have been the topic of frequent review, with findings identifying a multitude of concerns influencing the decision to either accept or decline participation.[6–8] More often, the literature has focused on key structural barriers such as cost and travel,[1] and the accessibility of trials suitable for an individual's cancer type and stage,[9] rather than potential psychological obstacles to participation. However, more recently there is an increasing body of evidence highlighting emotional distress and the psychological burden of a cancer diagnosis as a key inhibitor.[10–12] One problem is that patients are often asked to consider enrolling onto a trial at a significant psychological time point, for example, just after confirmed diagnosis. At such times, a cancer diagnosis combined with the implications of clinical trial participation can instigate significant psychological effects for both patients and their carer's.[13] Identifying and acknowledging the psychosocial needs of clinical trial participants can potentially be used as a means to increase and maintain participation. This discussion paper will review the psychological experiences and psychosocial barriers to patients participating in cancer clinical trials, not just at the point of recruitment, but throughout the trial episode. This paper will also discuss possible strategies for addressing psychosocial barriers which in turn may enhance the participation rate of cancer clinical trials in the future.

Methods

Three key electronic databases were searched for literature related to psychosocial aspects of participation in cancer clinical trials: CINAHL; PubMed; EMCare. The following search strategy was used: (((((distress × OR anxiety OR depress × OR stress OR needs OR psychosocial OR "psycho social" OR psychological OR holistic).ti, ab OR ("PSYCHOLOGICAL DISTRESS"/ OR exp ANXIETY/ OR DEPRESSION/ OR "STRESS, PSYCHOLOGICAL"/)) AND (("clinical trial").ti,ab OR exp "CLINICAL TRIALS"/)) AND ((participation OR participating).ti,ab OR exp "RESEARCH SUBJECT"/)) AND (cancer OR oncology).ti,ab). Titles of papers from the search were scanned to identify articles pertinent to the central aim. Duplicates and papers not meeting the inclusion criteria outlined in Table 1 were removed. The relevance of potential papers was determined by further scrutiny of each paper's abstract with reference to the inclusion and exclusion criteria.

The literature search yielded few results of high-level evidence research papers (for example, randomised-controlled trials) despite entering different search terms and key words. The majority of outputs were review articles. The literature review was further supplemented with a manual search. This was carried out by scrutinising the reference list of relevant papers in relation to the search criteria, yielding further articles to ensure other applicable studies were included. Commentary articles and anecdotal accounts were also included to add to the discussion.

Thirteen articles were included for discussion in the main review. This body of literature was reviewed and appraised using the appropriate Critical Appraisal Skills Programme (CASP) quality assessment tool.[14] The characteristics and main findings of the studies were extracted and reported. Key themes related to the central topic of the psychosocial barriers to cancer clinical trial participation were identified: anxiety and fear; ethnicity and social background; tensions between scientific objectives and personal motivations to participation; tensions between personal benefits versus altruism; carer perspectives. These formed the framework for the current discussion.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
Publication dates of papers between 2000 and 2020	Publication dates of papers pre-2000
Articles written in the English language	Articles not written in the English language
Full text accessible	Unpublished literature
Psychological or psychosocial patient factors	Articles not addressing patient's psychological or psychosocial needs
Articles related to participation in oncology clinical trials	Clinical trials not within or related to oncology

The Psychosocial Barriers to Cancer Clinical Trial Participation

Psychological concomitants to a cancer diagnosis

A cancer diagnosis can evoke a wide range of psychological responses, from natural reactions of vulnerability through to feelings of anxiety, fear, depression and spiritual crisis.[15–17] Furthermore, patients are commonly confronted by complex treatment options that are frequently imbued with uncertainty and mystification.[18] It is in this context that additional difficult decisions may be presented to patients if they are asked to consider the option to enrol in a cancer clinical trial.

Anxiety and fear as a barrier to participation

It is well established that anxiety and fear are frequently experienced by patients who have been diagnosed with cancer, sometimes referred to as 'cancer fear'.[19] Several authors have found fear applies not just to considering alternative treatment options, but to participation in clinical research.[7,20] A study by Quinn et al (2012), examined the role of fear in cancer patients' and their perceptions of clinical trial participation using semi-structured in-depth interviews.[21] Fear was experienced in several different contexts along the cancer pathway: the fear of the 'unknowns associated with cancer, cancer treatment, and clinical trials'.[21] Patients can lose a sense of control over their lives as they advance along the cancer therapy trajectory and begin to navigate their way through a network of medical appointments and procedures which now affect their day-to-day lives. In this study, some patients reported that the reason they declined participation was a way of assuming some element of control over their own health-related decisions. Although this paper raises some interesting insights and draws valid conclusions to fear as a potential barrier to participation, the study sample was conveniently selected. Participants who were interviewed ranged in age from 32 to 75 years (mean age = 66) and although had a diagnosis of different cancer types, the sample consisted predominantly of lung cancer patients. The authors do not acknowledge or specify if the treatment intent was palliative or radical. Results, therefore, may not be generalisable to all cancer patient populations and other clinical trial scenarios.

A recent systematic review by Sheridan et al (2020) found fear to be the leading barrier to trial participation in a large number of studies.[12] Often this was associated with the perceived risks of treatment and associated potential toxicities. However, the review also highlighted altruism in terms of contributing to science and helping others was a commonly reported factor.

Schaefer et al (2001) also found fear as a central theme in their study.[22] They evaluated the decision-making process by women considering participation in a breast cancer prevention trial. In this case, fear was not so much related to the cancer diagnosis, but associated with the uncertainty of the effects of treatment. However, Schaefer et al (2001) also identified some participants who, despite expressing fear, did not want others to experience the devastation of breast cancer and for this reason were, nevertheless, happy to participate in the trial.[22] So for some patients, fear was ultimately not a barrier to enrolment. There were other women in the study who expressed fear related to distrust towards the medical profession. This mistrust appeared to arise as a result of the process of discussing the extent to which they met the eligibility criteria to participate in the trial, which resulted in a lack of trustworthiness. There was a perceived arbitrariness about eligibility. The issue of trust between potential participants and healthcare professionals (HCPs) is discussed further below. In evaluating the results of Schaefer et al.'s (2001) study, it should be noted that there are some limitations. Firstly, the participants included in the study do not have a confirmed breast cancer diagnosis and findings cannot be directly compared to those that have been diagnosed with cancer. Secondly, all respondents were Caucasian women with a relatively high proportion educated to Masters Level, which may not reflect the true cancer population. Nevertheless, the paper was included in this review as it provides a rich holistic and valuable qualitative insight of the process of decision-making.

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Barriers related to ethnicity and social background

Another barrier to trial participation that has been found to be particularly relevant in relation to patients from black and minority ethnic groups is the fear and mistrust of HCPs. It has been noted that there is an underrepresentation of patients from ethnic minorities in cancer clinical trials.[23] In a review specific to minorities' participation in cancer trials, Salman et al. (2016) found fear and mistrust over the patient relationship with the HCP to be a key issue.[10] There were linguistic and literacy barriers giving rise to ineffective communication between patient and HCP. They also reported that cultural values, beliefs and stigma were a further concern. This was particularly highlighted by conflicting cultural beliefs in relation to herbal medicine or other complimentary therapies which may be contradictory with the scientific objectives of a clinical trial. This was found to lead to a resistance to participate in research.

Another social factor acting as a barrier to cancer clinical trial participation is the underrepresentation of poorer socio-economic groups, who appear to have more limited opportunities to participate.[24,25] Researchers seeking participants find such groups harder to reach. Conversely, patients from higher socio-economic groups have been found to be much more likely to enrol in cancer clinical trials.[26,27] An internet-based survey of 5499 patients, who were asked about their cancer treatment decisions, ascertained that income played a key role in the association of clinical trial participation.[28] Results from the survey indicate that discussion and participation of a trial were correlated with the participants of the younger, affluent and more highly educated population. In order for the results of clinical trials to be generalisable, the study sample and data collected needs to be representative of the general cancer population.

Ethnicity and socio-economic status can also intersect. Collectively, these factors can result in a lack of diversity within study samples and therefore potentially limit the generalisability of results to wider populations.[26] In summary, the research suggests that there are potentially inherent biases within participant selection in many cancer clinical trials, in particular in respect of ethnicity and socio-economic status. A related issue in oncology research undertaken in America is that potential participants might decide not to take part if they are unsure what the medical insurance implications of participation.[25]

Barriers related to randomisation: scientific objectives versus personal hopes

The methods used for scientific objectivity in a clinical trial may conflict with individual participant's personal motivations to take part. This is particularly evident in relation to the need for randomisation.[29] A common perception reported in the literature is misconceptions of being the subject of experimental testing, with some patients comparing clinical trial participation to being treated 'like a guinea pig'.[5] A large survey by Jenkins et al (2010) researched the attitudes of 1066 patients and their likely participation in a hypothetical two-arm randomised-controlled trial (RCT).[30] The concept of random assignment and leaving treatment decisions to chance was reported as a potential significant barrier to trial participation for patients. The results displayed a high proportion of patients (91%) were supportive of the notion that patients should be asked to take part in medical research. However, if treatment allocation was decided upon by randomisation, this figure dropped to 55%.

Harrop et al (2016) investigated the motivations, understandings and experiences of patients with advanced lung cancer who were participating in a non-placebo Clinical Trial of an Investigational Medicinal Product.[31] Ten participants from both the control and intervention arm of the FRAGMATIC trial were recruited to the integrated qualitative study (QualFRAG).[32] Participants were interviewed at up to three time points during their time in the trial to explore the psychological impact of participation in a clinical trial. Although it was reported that a generally positive view of participation in the FRAGMATIC trial was viewed, one of the interesting findings concerning randomisation, was that participants' understanding of the randomisation process was generally mixed, with many poorly comprehending the concept. Some patients understood and accepted the outcome of the randomisation. However, the study reported an extreme case where one respondent, who was randomised to the control group, was so 'disappointed and angered' by the result that they no longer wanted to continue taking part in the trial and refused further interviews. These negative emotional responses of allocation to the control arm ultimately lead to the individual's attrition from the trial. Although the authors were able to explore participants' concerns of randomisation in-depth, providing valid conclusions as to patients' understanding of random treatment allocation, some limitations to the findings should be highlighted. The participants were only interviewed once they had been allocated a treatment arm and therefore the study did not capture the potential shift of attitudes before and after treatment allocation. Furthermore, the study sample consisted of only ten participants, nine of which were male. Thus, conclusions cannot be drawn about other populations.

It is conceivable that the complex nature of RCT study design can contribute to patient misunderstanding and possibly deter patients from enrolling into cancer clinical trials. From the patients' perspective, in the context of life-threatening illness, it can seem a strange way to determine treatment.[32]

Hope: individual treatment benefit versus altruism

Although the literature highlights fear and anxiety as a barrier to participation to cancer research, it is worth addressing patients may also experience positive psychological outcomes of participation. Indeed, some authors have identified a key motivator for patients' enrolling in cancer research is 'hope'.[13,33] Chi (2007) considers hope to be an effective coping strategy, playing a significant role in aiding the cancer patient to adapt to their disease and treatment.[34] The notion of hope can change over time whereby people can transition from fear to hope.

One of the main themes in Dellson et al's (2018) interview study, which focused on patients with incurable cancer and their reasons to participate in cancer research, was the hope that they could overcome their cancer.[35] Some of the patients in this paper also reported an altruistic motivation whereby hope of recovery was not only in relation to themselves but for patients who may benefit from their participation in the future. In this respect, hope and altruism are intertwined. Similar findings were reported in a questionnaire-based study by Jenkins et al (2013), although in this case, the primary motivator for enrolment was altruism.[32] This contrasts with the results from a large cross-sectional survey by Truong et al (2011) where individuals identified the 'single most important' reason for choosing to participate in trials was to receive medical benefits and less likely for altruistic reasons.[36] For some patients, for example, individuals with a poorer prognosis or those entering earlier phase trials, altruism plays a less prominent role as a motivator for participation compared to expectations of personal benefit.[33,37]

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If taking part in an oncology trial has the effect of raising individuals hope for themselves, then that may imply a potential ethical concern for HCPs in how they promote the potential benefits of trial for patients. There needs to be an awareness of the possibility of raising unrealistic hopes. An additional related concern is that in raising hopes in patients, this potentially could undermine their autonomy in their decision-making as to whether to participate. It becomes critically important that informed consent is based on the realities of trial participation.

Carer perspectives

When exploring the potential psychosocial obstacles of recruitment into cancer research, it is important to also consider the perceptions of the patient's family or caregiver. Kim and Given (2008) acknowledge that cancer, and its consequential impact on quality of life, is increasingly recognised as a family's concern as opposed to solely the patient's with the diagnosis.[38] The authors determine family members and friends may be a source in providing 'informal cancer care', which can often involve meeting the individual's multi-dimensional requirements. This can include symptom management, psychological and psychosocial support, assistance with transport and possibly, financial support.[39] In such instances, the decision to enter a cancer clinical trial is rarely a decision made purely by the patient alone. In Bell and Balneaves' (2015) review, they identified several studies where recommendations from support networks (family and friends) as being highly associated with clinical trial participation.[5] Some research studies may require more attendances to the hospital, resulting in potential logistical challenges and requiring the support of family members. It is therefore important that the HCP promotes open discussion amongst patients and their caregivers when considering cancer trial entry and along the trial pathway.

Strategies and facilitators to improve participation

Healthcare professional communication and informed consent

The role and influence of the HCP can play a key part in facilitating intervention strategies to improve participation. A fundamental theme arising from much of the literature reviewed above is the importance of a trusting relationship between the patient and the HCP. This appears to be an overriding factor determining patients' decisions about cancer trial participation.[5] Albrecht et al (2008) found that the 'quality and quantity' of effective communication between the HCP and the patient influenced the patient's decision and decision-making process.[40] They particularly emphasised the importance of HCPs facilitating the building of a sense of alliance between patient and physician. The decisions made in cancer treatment, and indeed, the decision to enter a cancer trial is one that should be made autonomously by the patient. Understandably, the complex nature of study trial design can bring about challenges for patients and their families to actively engage in making such decisions. Albrecht et al.'s (2008) study identified that the patients who were noticeably engaged in interacting with their doctors were more likely to be engaged in clinical trial entry.[40] HCPs should therefore be aware of their influence in promoting patient-centred care, providing supportive communication and delivering medical content in a language that patients and their families from all backgrounds understand to enable the patient to feel empowered to make additional decisions about trial participation.

Dellson et al. (2018) suggested the decision to participate in cancer research is instantaneous and guided by emotion, significantly when based on a trusting relationship with the HCP.[35] In the light of the possibility of impulsive decision-making, it is crucial that full informed consent is nevertheless provided. Furthermore, care needs to be taken not to blur therapeutic and research ethics boundaries especially when securing informed consent. Researchers have a commitment to adhere to the principles of *Good Clinical Practice*, the international ethical, scientific and practical standard to which all clinical research is conducted to, as set out by the Health Research Authority (HRA) and underpinned in UK policy.[41] Reflective practice when applied to research is conceived essential to help manage those biases so it does not unduly influence the research outcomes.[42]

Psychological and psychosocial interventions

The objectivity of a cancer clinical trial is to test the efficacy and safety of a new therapeutic approach. Historically, cancer care and clinical trials placed more importance on physical toxicities and clinical outcomes over the psychological and psychosocial issues.[43] However, this approach has since shifted, and the importance of psychosocial care for cancer patients has become more critical, with emphasis highlighted in key clinical guidance where recommendations for routine screening to measure psychological distress should be carried out.[44] HCPs are in a key position to identify barriers and signpost to appropriate services.

Measuring toxicity utilises standardised nationally accepted systematic methods for reporting in cancer clinical trials.[45] Distress can be considered a psychological toxicity. Although there are some available standardised screening tools for assessing it, such as the National Comprehensive Cancer Network's *Distress Thermometer*,[46] they retain an element of subjectivity and therefore HCPs in this area of care may feel less confident in evaluating the significance of the outcomes. The National Institute for Clinical Excellence (NICE) has provided some guidance for HCPs, such as the *Model of Psychological Intervention*.[44]

Education and training

Those involved in clinical trials, particularly those leading clinical trials, need to be fully conversant with the factors that influence patient participation. There are specific areas of education and training which they and the research team may benefit from.[5] This in particular may include how to assess psychosocial concerns and distress and the application of standardised tools and evaluating the outcome of those assessments.

It is likely that if those involved in cancer clinical trials possess the qualities associated with an effective HCP, then they are also likely to be effective at addressing psychosocial concerns that potential participants might have. Advanced communication skills training for HCPs working in a research role within cancer care may be advantageous in providing HCPs with the communication and reflective practice skills to individualise their responses to patients' emotions and enable them to offer appropriate support when considering clinical trial entry.

Conclusion and Recommendations

Psychological responses to patients participating in cancer clinical trials can be a challenging issue to mediate. The research literature does not provide, at present, definitive clinical guidance. This is for several reasons: much of the research relates to different disease sites which may have differing prognoses; not all of the studies address the various phases of clinical trials. Furthermore, consideration has to be taken into account for

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various methodological limitations within studies undertaken to date. However, the research that has been undertaken does provide valuable insights.

The following key messages are identified. Firstly, there are many psychological and psychosocial factors impacting on cancer clinical trial participation. However, the psychosocial responses are not universally negative and for some individuals, a positive emotional response can act as a motivator to participation. Secondly, HCPs have a fundamental role in overcoming potential obstacles to participation in developing positive relationships with their patients. Thirdly, psychological assessments, although now more likely to be undertaken, could benefit from a more standardised and expert approach. There is a dearth of literature on existing established interventions in place to support patients and their decision to enrol in a cancer clinical trial. Further systematic research is warranted that considers these factors when developing effective interventions and strategies to greater understand patients' psychological and psychosocial needs to improve cancer clinical trial participation rates.

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