ETHICAL ISSUES AROUND PHASE I AND PHASE III CLINICAL TRIALS IN CANCER

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Abstract

The results of phase III (randomised) cancer clinical trials underpin evidence-based clinical practice. A standard comparator (control arm) is crucial so that the real value of an intervention can be tested. The goal of phase I trials is to assess the toxicity of a new drug and to determine the maximally tolerable dose to be recommended for subsequent studies to identify efficacy. Guidelines on informed consent intend to inform patients considering enrolment in clinical trials, but surveys of patients participating in cancer trials indicate that patient misunderstanding is common.

The current informed consent process commonly results in people enrolling in clinical trials without basic knowledge of the trials in which they are involved. Guidelines on informed consent intend to protect patients and promote ethical research conduct through full explanation of a proposed trial, including any possible harms and the requirement that participants freely consent. To give informed consent, participants should understand the purpose, process, risks, benefits and alternatives to research participation.[1]

Joffe et al measured the quality of understanding among participants in clinical trials of cancer treatments in Massachusetts to identify correlations of an increased understanding and to assess doctors' beliefs about clinical research.[2] They also reported evidence of therapeutic misconception in participants and doctors. They used an informed consent questionnaire (QuIC – Questionnaire Informed Consent) consisting of two parts to survey adult cancer patients who had consented to enrol in a clinical trial. Part A measures the knowledge of participants of informed consent specified in US federal regulations. Part B has 14 questions in which participants rate their understanding of important elements of the trial on a five-point scale. Response was averaged and normalised from 0-100 to generate a self-assessment score.

The QuIC was sent to 287 adult patients with cancer. Ninety per cent of respondents were satisfied with the informed consent process and most considered themselves to be well informed. Nevertheless, many did not recognise non-standard treatment (74%), the potential for incremental risk from participation (10%), the uncertain benefits to self (29%) or that trials are done mainly to benefit future patients (29%).

Methods of obtaining informed consent

Methods of obtaining informed consent evolved differently over the past 50 years without substantive information on the impact of these different practices on the patient. For clinical trials comparing randomised treatment, countries such as the UK and Australia in the 1980s allowed considerable latitude in what the patient was told. Simes et al undertook a prospective randomised study comparing two methods of obtaining consent for randomised trials of cancer treatment: a) an individual approach where the amount of information given to the patient was left to the discretion of each doctor and consent was verbal; and b) a uniform policy of total disclosure of all relevant information relevant to the clinical trial, both verbally and in a written consent form.[3] The main endpoints of the study were the effects of the two consent procedures on patients' willingness to participate in clinical trials, on their understanding of their illness and treatment, on their anxiety levels, and on their perceptions of the doctor-patient relationship.

The main effects of total disclosure compared with an individual approach were: a better understanding of treatment and side-effects and of research aspects of the treatments; less willingness to agree to randomised treatment; and increased anxiety. A repeat questionnaire given three to four weeks later no longer showed significant differences between the groups. We concluded that results clearly indicated some trade-offs when patients are given all the relevant information compared with an individual approach to obtaining consent. We hoped that our result would stimulate similar control trials of consent practices at other hospitals where the style of seeking consent may differ, but this did not eventuate and detailed written consent is now required in almost all studies on humans in the western world.

Interventions aiming to enhance informed consent

Jefford and Moore analysed the written consent form and the discussions that had taken place between clinician or investigator and patient.[1] They reviewed strategies to improve consent forms, particularly the use of plain language. Recommendations were made on discussions between investigator and patient to improve patient comprehension and satisfaction. They comment that the discussion should first include a discussion of standard treatments, followed by discussion of potential treatment as part of a clinical trial. They recommend that the patient, according to their preference, be given written information or a recording of the conversation, or both. Delaying of consent (e.g. overnight to digest what has been said and to read the written consent documents) may increase satisfaction with participation and improve understanding. Checking of understanding and asking patients whether they have any questions and offering time to think about the information and discuss with others was recommended.

Resnick has argued that despite extensive critiques of informed consent documents, there are ethical and legal reasons why they cannot be replaced by conversations with study personnel as the chief vehicle for obtaining seeking consent from patients.[4] The possible role of patient decision aids to complement the consent documents and to inform the conversation with the potential clinical trial participant has been advanced.[5] We developed a cancer clinical trial question prompt list (Question Prompt List, Clinical Trials, QPLCT) Brown et al to inform the clinical trial conversation and empower the patient to ask questions.[6] We have conducted a randomised clinical trial of a QPLCT, and the manuscript is under review.

Outcomes reported in trials of interventions to enhance the informed consent process have focused on understanding of trial information. Outcome measures and issues such as decisional conflict, trust, coercion, honesty and patient involvement have been largely ignored. The wider features of randomised trial decision-making and interventions intended to improve them merit more extensive investigation.

Audio recording informed consent discussions

We audiotaped 59 consultations in which 10 participating oncologists sought informed consent.[7] Transcripts were analysed using a coding system to identify the presence or absence of aspects of four domains for ethical communication about phase II and III clinical trials, namely: shared decision, sequencing information; type and clarity of information; and disclosure/coercion. Oncologists rarely addressed aspects of shared decision making, other than offering to delay a treatment decision. Moreover, many of those discussions scored poorly with respect to ideal content. Oncologists were rarely consistent with the recommended sequence of information provision. A rationale for randomising was only described in 46% of consultations. In 29% of consultations, oncologists made implicit statements favouring one option over another, either standard or clinical trial treatment.

Jenkins et al analysed 82 audiotaped discussions during which consent was sought for enrolment in a randomised clinical cancer trial.[8] In most interviews the concept of the trial was introduced by describing uncertainty about treatment decisions – all oncologists used the word 'trial,' but randomisation was used in only 62% of discussions. The median duration of 'consent' interviews was less than 15 minutes, and most patients signed the consent document at the first consultation when the clinical trial was discussed.

Audiotaping informed consent consultations has informed development of interventions to assist oncologists in seeking informed consent to cancer clinical trials.[9] The notion that patients receive a copy of the taped informed consent discussion merits investigating, particularly now that a high proportion of patients carry their own smart phone.[10]

The consensus opinion of ethicists, linguists, health professionals and consumers was that standard treatment options (including no treatment) should be discussed first and the doctor's recommendation should be provided before the clinical trial is introduced as another treatment option. Furthermore, doctors should routinely explain the sources of medical knowledge and the levels of evidence for the standard treatment options.[11]

Phase I trials of new cancer treatments

The first evaluation of new cancer treatments in human subjects occurs in phase I trials. Phase I trials are not designed to demonstrate tumour response. Their aim is to define the safety profile and to identify appropriate phase II trial drug doses and schedules. The rate of tumour response in phase I trials is estimated at less than 6%, with a toxicity related death rate of about 0.5%.

Tomamichel et al reported the process by which patients were informed and their consent obtained in phase I trials.[12] The procedure consisted of three consecutive conversations in which the investigator, the clinical trial research nurse and the patient's relatives or friends also participated, followed by the patient signing of a written consent form. Thirty two conversations were audio-recorded, transcribed and evaluated by one psychiatrist and one psychologist. A quantitative analysis of information provided was undertaken by calculating the percentage of patients to whom six items of information considered essential by the team had been conveyed. The qualitative analysis was performed by rating on a five-point scale (1-5, bad to excellent) the three dimensions

of the informing process for each patient. Complete information about the characteristics of the phase I drug and treatment and follow-up was given to 80% of the patients. All but one of the information items scored well (>3.5), with the one related to the assessment by the doctor of the patient's understanding at the end of the consultation scoring <3 in 53% of patients. The authors concluded that physicians should become more skilful in providing adequate information and improve the delivery of information.

People enrolled in phase I clinical trials often equate medical research with medical care. Meropol et al described and compared the perceptions of cancer patients and their oncologists regarding phase I clinical trials in the US.[13] Three hundred and twenty eight patients enrolled in phase I trials and 48 oncologists completed surveys, with domains including perceptions of potential benefits and harms from treatment, both experimental and standard, relative value of quality and length of life, and perceived content of patient oncologist consultations. Patients had high expectations regarding the outcome of treatment, with a median 60% benefit from experimental therapy. Patients predicted a higher likelihood of both benefits and adverse reactions than their oncologists. The authors concluded that the discordant perceptions of patients and oncologists may be explained by patient optimism, but there is also the possibility that communication between oncologist and patient is suboptimal. Jenkins et al evaluated the communication and informed consent process in phase I clinical trial interviews in the UK.[8] In several important areas, information was either missing or was interpreted incorrectly by patients. Discussion of prognosis was frequently absent, but alternatives to phase I treatment were explained.

Catt et al recruited patients considering phase I cancer trial enrolment to complete a 19 item study specific 'accept or decline' measure exploring hope, expectations of benefit, altruism, concerns and general perceptions of the trial information.[14] Patients were generally optimistic, and 90% consented to trial entry. However, 51% thought the trial was the only treatment option available. The four main reasons for trial entry were expectation of some medical benefit (21%), trial the best available option (21%), to maintain hope (15%) and to help research (13%). The authors concluded that achieving genuine informed consent and avoidance of therapeutic misconceptions in phase I trial patients may be difficult.

Pentz et al interviewed and surveyed phase I trial participants at an academic centre in the US and explored therapeutic misconception – misunderstanding of the research purpose or how research differs from individualised care, and therapeutic misestimation – and found misestimates of the chance of research trial benefit as greater than 20% or underestimates of risk as 0%.[15] Sixty five of 95 respondents (68%) had therapeutic misconception. Risks novel to research of requiring biopsies were rarely mentioned (3%). Most respondents thought their chance of benefit was higher and risks lower than the population chance, with 55% optimists, and 38% pessimists.

It seems that patients enrolled in phase I clinical trials often equate medical research with medical care and misunderstand the risks and potential benefits of participation in a phase I trial. Although clinical trial consent forms explain how a clinical trial will differ from standard care, the details are not succinctly addressed in the consent form.

Miller and Joffe discuss the ethical concerns raised about the quality of informed consent by participants in phase I cancer trials.[16] These concerns revolve around three dimensions: therapeutic misconception; therapeutic misestimation; and unrealistic optimism. They consider whether the observed defects in understanding and appreciation call for improvements in the process of obtaining informed consent for phase I trials. Do these defects invalidate consent? They agree that although investigators must enhance participants understanding of what phase I trials involve, the three types of misunderstanding concerning the "purpose, methods and personal risk-benefit ratio of the trials - do not necessarily render the consent of trial participants invalid."

Phase I trials in children with cancer

The informed consent process for research trials can be particularly difficult in children and adolescents. Miller et al describe hopeful and persuasive messages by paediatric oncologists during informed consent conferences.[17] Participants were children with cancer who were offered a phase I trial along with their parents and physician. The conferences were audio-recorded, and coded for physician communication of hope and persuasion. Parents completed an interview (n=60). The most frequently hopeful statement related to expectation of positive outcome, and mention of treatment options. Physicians did not mention 'no treatment' or palliative care in 68% of the conferences, nor that the disease was incurable in 85% of the conferences. Hopes and goals other than cure or longer life were rarely mentioned. A minority of the physicians stated that the disease was incurable. The authors comment that physicians have an important role helping families develop alternative goals when no curative options exist. Questions for investigation include the variability in how physicians describe phase I trials, and the relationship between the content and process of communication during informed consent conferences. Strategies to reduce physicians' 'unbalanced' presentation of the purpose and benefits of phase I trials are necessary. They observe that tempering hope with realism is one way to be compassionate with patients and families while supporting informed decision making at the end of life.

Baker et al completed interviews with a total of 57 parents and 20 patients aged 14-21, who had the option of participating in a phase I paediatric oncology clinical trial.[18] The transcribed interviews were studied using established content analysis methods. Twenty one unique suggestions for improvements were made in three themes: provision of more information, structure and presentation of the informed consent process, and suggestions conducting the process. Physician investigators should be familiar with these recommendations and interventions incorporating them should be investigated.

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