CLINICAL INVESTIGATION

Ethical issues in adult oncology randomized clinical trials

Clin. Invest. (2011) 1(5), 629–636

Randomized clinical trials (RCTs) are essential to evaluate novel cancer interventions and to improve care and outcomes. Conducting clinical research in oncology conveys ethical obligations to safeguard the interests of research participants and to ensure that they are an informed partner in our efforts to improve cancer care. Core ethical requirements of oncology RCTs are: asking a good question and designing a trial that can answer it; ensuring the voluntary informed consent of participants; and promoting the safety and interest of research participants at all times. This article will review some of the major ethical issues that arise in the course of design, conduct and analysis of oncology RCTs.

Keywords: cancer • clinical trials • ethics • informed consent

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Although there have been many advances in oncology in recent decades, cancer still causes over 7.5 million deaths worldwide each year and more effective interventions are needed in many settings [1]. Clinical trials are required to test the most promising new interventions and to determine which are safe and effective for use in routine clinical practice. This process, critical to improving outcomes for future patients, is dependent upon current patients agreeing to receive care in a setting that may expose them to risks of unproven interventions, unknown toxicities and procedures, and tests intended only for research. The design and conduct of cancer clinical trials thus carries special ethical responsibilities to safeguard the interests of research participants and ensure that they are an informed partner in our efforts to improve cancer care. Standards of medical ethics and regulatory codes for protection of human research subjects require that the rights and interests of trial participants be considered and protected before, during and after the conduct of research. This article will review some of the major ethical issues that arise in the course of oncology clinical trials, focusing on issues that arise in the last stage of testing novel interventions, the randomized control trial (RCT).

Ethics considerations in trial design

When proposing to test a novel cancer intervention among patients who actively need treatment, it is important to understand that, by definition, we are subjecting the participants to unknown risks and benefits, and in some sense, using people as a means to scientific ends. The most important ethical principles in clinical research are to ensure that:

- The scientific question we seek to address is worth asking;
- We take steps to protect the safety of the trial participants and to ensure, to the extent possible, that any intervention used within a trial has at least as good a chance to benefit the patient as any standard intervention;
- That trial participants make informed and voluntary decisions to participate in the study;
- That trial participants understand that they are participating in research, which has scientific goals, independent of any goals to benefit individual participants.

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One of the first principles of ethical clinical research then is that ethical studies start with good science [2]. Long before the first patient is approached to consider trial participation, concerns over protection of research participants must be considered in the process of trial design. Considerations arising during trial design include selection of an appropriate patient population, determination of the experimental regimen, and development of a monitoring plan for both common and rare toxicities that maximizes participant safety throughout the trial. In addition, RCTs require a selection of appropriate control interventions, (including placebo controls in some cases), determination of appropriate intervals for interim analyses, specification of stopping rules and consideration of whether an independent data monitoring committee is needed.

Among the first decisions in the design of any RCT is determination of the experimental and control regimens that will be compared. Although risk and uncertainty are inherent in clinical research, risks to research participants must be minimized. Minimizing risk in this context requires that the interventions selected be at least roughly equivalent to the best standard care the patient could receive outside of the trial, based on available evidence. The challenge of course, is that if we knew the relative safety and efficacy of the interventions in an RCT, we would not need to perform the trial. We design oncology RCTs with the hope that the experimental arm will prove superior, while knowing that despite promising data from early phase trials this is often untrue and, on very rare occasions, the experimental arm will prove inferior [3]. The term 'clinical equipoise' is used to describe a situation for which, based on available evidence, there is uncertainty within the medical community over whether an experimental intervention is likely to be superior, inferior or equivalent to a standard therapy [4]. If we can accurately claim that there is clinical equipoise among the arms of a given trial, it is considered ethical to randomly assign participants to any of the trial interventions. There is active controversy in the ethics literature regarding the concept of equipoise, but it continues to serve as a commonly understood framework for how we justify randomization in cancer clinical trials [5].

One possible means to ensure that all participants in an RCT receive care that is at least equivalent to standard therapy is to simply design a trial that compares a standard control treatment to the same treatment plus the experimental intervention. This strategy is often used for novel molecularly targeted agents when the mechanism of action and/or preclinical data suggests they will work most effectively in conjunction with more standard cytotoxic agents. An additional strategy often employed to broaden access to an experimental intervention is the crossover design, where a patient is allowed to crossover to the experimental regimen following a prespecified interval or end point. Although this clearly expands access to experimental interventions, it may complicate the evaluation of important end points, such as overall survival.

In trying to address a meaningful and potentially practice changing question, both the standard of care and preclinical (or early clinical) evidence for synergy with the experimental intervention must be taken into account. Failure to consider the current standard of care may leave clinicians uncertain of how to interpret the results of an otherwise positive study. Alternatively, failure to wisely select both the therapeutic backbone for the intervention and the correct patient population could lead to negative results for an intervention that may have been effective in a different context. Both consultation with clinical experts in the field and substantial scientific evaluation of the proposed experimental regimen are required before taking an intervention forward into a Phase III RCT in order to best serve the goals of science, the interests of trial participants and wise use of financial resources.

The role of placebos in oncology randomized trials

One issue that frequently arises in oncology RCT design is the question of placebo controls. As above, patients with cancer often face a risk of recurrence or death without effective treatment, thus the use of an inactive agent in a RCT deserves scrutiny. However, as reviewed in detail by Daugherty *et al.*, placebo's may be appropriate in oncology RCTs under several conditions [6]. In settings where there is a proven standard intervention, use of a placebo alone as a control intervention is not ethical. However, use of a placebo in addition to standard therapy, such as an RCT of chemotherapy plus experimental drug versus chemotherapy plus placebo, can be ethical because patients in the placebo arm are still receiving appropriate care. In settings where there is no proven intervention and forgoing disease-directed therapy is considered a reasonable option, a placebo control may be ethical. A placebo control could be considered in the adjuvant setting if no intervention is proven to reduce the risk of recurrence, or in the late line metastatic setting when there is no evidence for further disease-directed therapy (although palliative care should still be provided). Use of a placebo may make RCT design more ethical if it ultimately improves our ability to address a scientific question (such as making a more valid assessment of the benefits or toxicities of a novel intervention) and does not deprive patients of a proven therapy. In oncology, patients should always be informed if there

is potential for them to receive a placebo in an RCT, and the nature, justification and consequences of this intervention should be clarified.

Need for appropriate sample size & opening studies that can succeed

An issue that may be overlooked in the planning stages of an RCT is the need to ensure that that individual trial centers, oncology research networks or cancer cooperative groups only develop and/or open studies that have a reasonable chance to efficiently complete accrual and provide an answer to the scientific question addressed by the trial [7]. There is a need to ask not only whether the trial is well designed and important, but also is it important in comparison to other studies that are currently competing for the same population of patients or studies evaluating different interventions that could be opened as an alternative? In most areas of oncology, there are abundant clinical questions that could be addressed through an RCT, but limited financial resources and finite numbers of eligible patients. As a result, sample sizes for RCT must be sufficient to address the scientific question, but no larger than needed. Underpowered studies expose patients to harm without adequate chance of societal benefit by advancing knowledge [8]. Conversely, overpowered studies may waste finite resources, take longer to accrue and expose more patients to possible harm than necessary to answer a question.

The US Institute of Medicine recently published a critique of NCI-funded cooperative trials, which have, at times, enrolled thousands of patients but failed to answer a meaningful question owing to either inability to complete accrual or inefficiency that resulted in the clinical question becoming outdated by the time the results are available [7].

The focus on sample size and trial accrual must coincide with the development of an ethical recruitment strategy. Payments to both physicians for recruiting patients and direct payments to patients for participating in clinical trials are controversial, raising concerns over conflict of interest (among physicians) and undue incentives that violate the principle of voluntary informed consent (among patients) [9,10]. Relevant factors in considering the ethics of providing financial incentives to research participants include the risk of the study [9]. Given the narrow therapeutic index of many oncology interventions, payments beyond compensation for expenses incurred as a result of participation will likely remain rare in oncology RCTs.

Additionally, there is increasing concern that trial participants are not representative (on the basis of race/ethnicity, gender and age) of the broader patient population with the disease in question [11–13]. It is particularly important in Phase III trials, that may define the role of an intervention in standard practice, to attempt to recruit a diverse and representative patient population. The race/ethnicity of trial participants should be recorded and reported so that the impact of the intervention on groups facing cancer health disparities can be evaluated [14].

The importance of correlative science

Increasingly, we want to understand not just if a drug works, but also why or why not, and which patients are most likely to respond. Correlative science seeks to identify molecular features of a cancer that are associated with response or resistance to therapy. Such research often requires tissue, either from blood samples or tumor biopsies and introduces an additional set of ethical concerns into the conduct of clinical trials. For many correlative questions, an archival tumor sample or a blood sample is all that is required and the primary issues raised relate to informed consent and protection of the participants privacy, particularly when genetic information will be obtained [15]. However, when tumor tissue is required and no adequate clinical sample is available, then a biopsy solely for research purposes must be performed. Research biopsies raise additional ethical concerns by virtue of subjecting the trial participant to some degree of additional risk from an invasive procedure, in exchange for little or no chance of direct personal benefit (depending on the trial design and whether biopsy results will be used to guide further therapy).

Some of the greatest controversy in this area has arisen surrounding the use of mandatory versus optional research biopsies in clinical trials [16]. Proponents of mandatory research biopsies in cancer clinical trials argue that in some cases tissue samples from all participants in a clinical trial may be necessary to answer a critical scientific question. It could be argued that in such cases, it is unethical to conduct an RCT without obtaining tissue to address the correlative question that is needed to truly move the field forward, particularly in an area of oncology where standard therapy offers no realistic hope of cure. Opponents of this view argue that adequate information can be gained from voluntary biopsies among those who provide additional consent and that linking research participation to willingness to undergo a biopsy creates an unfair barrier to access experimental interventions and violates the principle of voluntary informed consent. While this is not a settled issue, at least one NCI Cancer Cooperative Group has produced a white paper arguing that mandatory research biopsy can be justified under select circumstances and proposes guidelines for trials with a mandatory biopsy design [16].

The ethical considerations regarding tissue and correlative science samples extends beyond issues surrounding their acquisition to concerns regarding genetic testing, indefinite storage and future use, and rights to future discoveries. The Health Insurance Portability and Accountability Act of 1996 has helped address issues of privacy surrounding genetic testing and storage as it mandates de-identified banking and outlines strict rules regarding use.

Ongoing efforts seek to improve informed consent language for correlative science, biobanking and future use of tissue [17]. The importance of these issues are highlighted by the recently publicized case of Henrietta Lacks and the story of groundbreaking research that was conducted from cell lines derived from her tissue (HeLa cells) without the consent of the patient or her family [18].

Trial conduct

Beyond issues surrounding the design of clinical trials, the scientific conduct of these trials raises ethical concerns in the arenas of accrual, monitoring and data collection. We need to carefully consider how we recruit patients to oncology RCTs, how we ensure good care and safety throughout the trial, and how to respond when challenges emerge for individual patients or the trial as a whole.

Informed consent

The ethical foundation for clinical research relies on the voluntary informed consent of research participants. Elements of informed consent that must be disclosed and explained to all patients, as defined in federal regulation in the USA [19] are described in Table 1. It is important to recognize that there is a difference between the process of providing consent and achievement of actual informed consent among potential research participants. Measuring, let alone ensuring, understanding among trial participants is unfortunately complicated. There is currently greater consensus on details of the process for providing informed consent, including development of an informed consent document that is approved by an Independent Review Board than on the importance and feasibility of achieving truly informed consent [20].

Ethicists have been particularly concerned with potential for 'therapeutic misconception' whereby trial participants falsely assume that all elements of a clinical trial are done with therapeutic intent to benefit the individual. While the degree to which this is a problem in oncology RCT is unknown, it is important for those conducting clinical research to be aware of this controversy and to strive to ensure that research participants understand the scientific goals of research and consent to any elements of trial care intended for research purposes only [21].

In oncology trials, specific populations that may not be able to provide informed consent due to mental capacity or freedom from potential coercion are typically excluded from research, such as patients with severe psychiatric disease or incarcerated patients. Capacity for voluntary informed consent is also a concern among some populations who are frequently considered for oncology RCTs, including children and patients with terminal illness [22,23].

Managing care for trial participants

Once a patient is enrolled, the primary ethical obligation within an RCT is to ensure that the participant is monitored appropriately and given the best chance of a good clinical outcome with minimal toxicity. Investigators may be faced with circumstances in which the interests of the individual trial participant appear to conflict with the goals of the study. This can arise in the setting of toxicity that, in the clinician's judgment, requires a change in therapy in contradiction to that which is defined in the protocol. Safety measures within the protocol, including defined dose adjustments or limits on concurrent medications, should be carefully considered to protect the participants' interests. However, when conflicts arise in the course of research the interests of the participant should always trump the interests of the science as required by the Declaration of Helsinki [24].

As previously noted, patients must be informed prior to the initiation of research of their ability to withdraw from a clinical trial at any time. If a patient experiences toxicity, or simply wants to stop participation in a trial, the investigator must respect this decision and facilitate ongoing appropriate care outside of the RCT.

Interim analyses

In the 1960s Data Safety Monitoring Boards (DSMBs) were pioneered as an instrument for monitoring interim data generated by clinical trials to ensure safety to the participants [25]. DSMBs have grown and are now widely used as an independent review board composed of knowledgeable individuals with no conflict of interests to protect the safety of participants and to review safety and efficacy data as they become available. DSMBs deal with many ethical issues including the scientific integrity of trials, when to stop a trial early based on a favorable or unfavorable interim analysis as well as evolving clinical science external to the trial and the degree of sharing that should occur with trial participants when a trial is stopped prematurely [26].

One of the most complex issues that can arise during analysis of RCTs is the question of how to respond to interim analyses that suggest, but do not conclusively prove, that one treatment arm within an RCT is likely

Table 1. Elements of informed consent adapted from the USA code of Federal Regulations for Human Subjects Research.

Issues to address	Details required for informed consent
What does the study involve?	Explain that the trial is research and describe in sufficient detail the interventions that the participant may be exposed to, method of determining which intervention they will receive, and clarify which parts of the intervention are considered experimental and unproven
What are the risks and possible benefits of study participation?	Explain the known risks and toxicities of any interventions, including life threatening risks, and clarify the uncertainties regarding safety and efficacy. Explain the nature and degree of benefit that might reasonably be expected based on existing data
What are the alternatives?	Describe alternatives to trial participation, including receipt of standard therapy outside of the trial. Where appropriate (such as metastatic cancer), this should include the alternative of no disease-directed treatment, with a focus on palliative care
How will information from the participant be used and who will have access to this information?	Explain and disclose how personal health information will be used, how information will be kept confidential, and who will have access to this information
How will illness or injury as a result of trial participation be handled?	Explain the procedures for handling illness or toxicity that results during the course of the randomized clinical trials, including the responsibility, or any limits on responsibility, of the treating physician and the trial sponsor
What are the consequences of not participating?	Explain that participation is voluntary and refusal to participate will not involve penalty or loss of benefits to the patients. Explain that withdrawal of consent or discontinued participation at any time will not incur a penalty or loss of benefits
How will new information that arises during the study period be handled?	Explain that new findings discovered during the course of research, which may affect the subject's willingness to continue participating, will be provided
Under what circumstances would the participant be taken off of the study?	Explain the situations in which the participants will be forced to stop participating (i.e., disease progression, laboratory abnormalities and so forth). Explain the end of study procedures and who will direct consideration of further therapy after the trial

Adapted from [19].

to be superior or inferior to another. One well recognized example is the Prostate Cancer Prevention Trial, in which thousands of men were randomized to finasteride or placebo for the prevention of prostate cancer [27]. At interim analysis, the independent DSMB identified an unanticipated absolute increase in the incidence of high-grade prostate cancer among finasteride recipients amid an apparent overall prevention benefit from the drug. The question was whether to stop the trial, continue the trial with or without informing participants of the emerging data or to inform patients and require re-consent. This type of information, which was both preliminary and carried potential safety consequences for trial participants, raised questions of how we balance our obligations to promote the safety of research subjects, scientific integrity and the ethical integrity of our research enterprise [26].

Interim analyses can also suggest superior efficacy for an experimental intervention leading to consideration of stopping an RCT early. The decision to stop the MA-17 trial of letrozole following tamoxifen for breast cancer after 2.4 years of follow-up (when virtually no patients had received the planned 5 years of experimental therapy) supported approval of the drug in this setting, but led to criticism that the optimal duration of therapy, toxicity and long-term risks could not be established [28].

Considerations when debating the course of action following an oncology RCT interim analyses include:

- The nature of harm or benefit being considered
- The cost to research participants and to future patients if no further trial information is obtained
- Whether withholding results of the interim analyses is consistent with the consent of research participants [26]

Final analysis & presentation of results

Analysis of RCT results is critical to establish whether an experimental intervention should be used in routine oncology practice and, if so, under what conditions. As such, integrity in data analysis and unbiased interpretation of results regarding safety and efficacy are essential to promote the interests of future patients who may be considered for the intervention in question, and to further respect the contribution of trial participants. Short

of deliberate fraud, which clearly undermines scientific credibility [14], ethical issues that may arise during this stage of research include:

- Integrity and accuracy in data analysis
- Management and disclosure of conflicts of interest (COI) on the part of investigators
- Transparent reporting and widespread dissemination of RCT results

Policy on disclosure and management of COI is rapidly evolving. When scientific investigators are direct employees or receive financial support of any kind from pharmaceutical industry sponsors of RCTs, there is potential for bias in analysis or reporting of results. At minimum, most scientific journals, meetings and academic institutions now require disclosure of any potential conflicts and, increasingly, such conflicts are made publically available. Whether and to what extent some types of conflicts should be prohibited, and how broadly potential COI should be defined, remains an area of active debate. It is important to recognize that COI include scientific as well as financial conflicts. Investigators may have academic incentives to produce positive results that outweigh any direct financial consequences of a trial. A mechanism to reduce the potential for bias as a result of COI is to ensure access to data and reviews by independent investigators with no direct stake in the outcome, such as independent evaluation of radiographic or pathology data, DSMB review and/or peer review.

In addition, it is important to report all major results of RCTs, whether they are favorable or unfavorable. Positive RCT results are more commonly associated with trials sponsored by the pharmaceutical industry than with non-industry trials [29,30]. This could result from biased analysis or presentation of data, selective publishing of positive studies, selection of inappropriate controls, or due to more careful selection of interventions to take forward into RCTs resulting in a truly higher rate of success. Recent requirements to register trials in large databases will improve our ability to evaluate the reasons behind this association in the future. From an ethical standpoint, investigators must be aware of the need to present and publish negative results, which although less glamorous can be important to advance the field.

Ethical issues after a trial is conducted

Patients participate in RCTs both to gain direct personal benefit and to help others. On both counts, trial participants have an interest and right to expect that the outcomes of trials will be available to them. Public release of data does not guarantee that trial participants will be informed or that the information will be presented in an accessible fashion. Failure to directly share trial results occurs for multiple reasons including limited resources, uncertainty of patients' wishes and, in some cases, fear of creating anxiety in participants of negative trials. Partridge *et al.* demonstrated that sharing results is feasible and meets with a high degree of participant satisfaction, even when the trial results are negative [31]. Clinical researchers should be aware of the importance of this issue, and ideally should consider how to best share results with trial participants at the time of trial design [32].

Questions of access to promising new interventions may also emerge once a trial is completed. In some cases, the experimental intervention may be superior to standard therapy, but not widely available. Expanded access programs, although imperfect, have been created to address this concern and need. Such programs typically emphasize an ongoing need for informed consent, safety monitoring and, ideally, ongoing data collection that can teach us about the impact of the drug in a broader population than tested in the RCT.

Conclusion

Trials are essential to test the efficacy and safety of promising experimental agents, but rely on a firm ethical foundation from the moment of inception to presentation of results. Patients with cancer considering enrollment in clinical trials expect that their interests as patients will be respected, that the scientific questions addressed by the trial will be important and that the trial will be well designed to answer those questions. Although attention to the issues raised above regarding trial design, informed consent, safety monitoring, analysis, and reporting of results, the ethical basis for the partnership between trial participants and clinical investigators can be maintained and strengthened in the interest of both current and future patients with cancer.

Future perspective

Many of the bedrock principles of ethical research and protection of research subjects are unlikely to change. However, emerging issues include costs of clinical research and establishing the appropriate balance between regulation and innovation in cancer research, as in other areas. We will need to address current practices, such as the informed consent process, procedures for biobanking and correlative studies, and data safety monitoring, and ask if they are truly meeting the goals of informing and protecting research subjects and how we might improve. In addition, as financial and efficiency issues lead to more cancer clinical research in both the developing world and in the community oncology setting we must try to understand the consequences

of these changes and ensure that high standards for the science and ethics of clinical research are maintained in all settings.

Financial & competing interests disclosure

Jeffrey Peppercorn discloses the following: Genentech (honoraria), Novartis (research, honoraria, consulting) Aveo Pharmaceuticals (consulting), GlaxoSmithKline (spouse employment). Jeffrey Peppercorn is also supported by the Greenwall Foundation for Bioethics and the American Society of Clinical Oncology Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Key ethical principles of oncology research are to ensure that the trial is well designed to answer an important scientific question, that participation is informed and voluntary, and that the interests of research participants are considered, respected and protected at all times.
- Ethical considerations in oncology randomized clinical trial design include ensuring that best standard therapy or an intervention believed to be superior or equivalent to standard therapy is offered in all trial arms.
- In evaluating interim results, balancing the benefits of stopping a trial that appears to demonstrate superiority of one treatment arm compared with another must be balanced against the scientific interests of obtaining sufficient power and longitudinal follow-up data to ensure that the results are validated and reliable.
- Ethical issues persist after completion of a clinical trial and focus on accurate presentation of results and communication with participants regarding research results.

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