# Clinical trial design in oncology

## Protocol design

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A clear, well-designed protocol is the core of a clinical trial. The protocol describes the objectives, design, methods, statistics, and organisation of the trial, as well as its background and aims—a good trial protocol addresses an important unanswered question. The type and phase of a clinical trial defines many specific parts of the protocol: clinical trials that include surgery or radiotherapy need in-depth explanation of the procedures for quality assurance and control, especially if these methods are part of the trial hypothesis.

The International Conference on Harmonisation document ICHE6, *Good Clinical Practice*, is a reasonable framework for the design of a good trial protocol.[1] This framework addresses various important issues such as ensuring regulatory compliance, which in European countries would involve implementation of national legislation for the European Union Clinical Trials Directive. Protocols for randomised trials that enable reporting of results according to the CONSORT (consolidated standards of reporting trials) statement is best practice.[2] Although CONSORT is an accepted worldwide standard, the present regulatory environment means it is important to consider early on which countries will be involved in a multicentre, transnational trial. Although there should always be only one protocol for a clinical trial, US–UK intergroup trials need separate sections on specific national requirements for good clinial practice, trial management, and pharmacovigilance. Despite talk of worldwide regulatory harmonisation, the reality for the foreseeable future is different national requirements between countries. Development of the trial protocol should use the expertise and input of patients, statisticians, site-specific clinical groups (eg, the UK's National Cancer Research Institute Clinical Study Groups), and members of the clinical community outside the immediate circle of the main investigators. Identification of major issues before the trial, such as ensuring that the comparator regimen is acceptable to all members of the trial group, can save substantial time and effort later when major changes to the protocol need authorisation from regulatory authorities and ethics committees.

Early sections of a protocol should set out general information, including the unique identifier numbers from trial registration (ISCTRN) and EUDRACT, a unique number allocated by the new European pharmacovigilance database. Protocols for consideration by the UK public funders of cancer research (the joint Cancer Research UK/Medical Research Council Clinical Trials Awards and Advisory Committee) should include preclinical and clinical justification for the proposed clinical trial in the section on background information. Clinical justification should include data from a systematic review, if appropriate. More complex and detailed data are needed to justify pivotal first-in-man phase I/IIstudies of new molecular entities, and a separate information brochure detailing all preclinical data will be needed.[3]

Many trials fail because of design flaws, and special attention should be given to the biostatistical section. Failure to address inclusion and exclusion criteria for trial entry adequately weakens many protocols because the results have little applicability in the real world. For example, too many trials exclude patients who are elderly without any scientific justification.[4] Furthermore, careful scientific and clinical scrutiny of entry criteria would help increase the number of trials available to patients and the recruitment rate.[5] The design of randomised trials should, at a minimum, involve the expert input of a biostatistician who follows the CONSORT statement. Biostatisticians can use other standards of protocol design such as ICH9, which is favoured by the pharmaceutical industry.[6] Several statistical methods have been developed for phase I and multiphase II trials, including the well known methods of Gehan from the 1960s and Fleming in the 1980s.[7] Irrespective of the trial phase, a full description of the appropriate statistical design in the trial protocol is crucial. For randomised trials, this description should include early-stopping rules and a priori subgroup analyses. Endpoints of a clinical trial should be considered carefully to ensure they are both clinically meaningful and achievable within the limits of the trial design.[8]

In Europe, the implementation of the Clinical Trials Directive has meant that it is now crucial for protocols from the non-commercial research community to address issues of trial management in the protocol. Consideration should include, when there are multiparty sponsors or divisions of trial responsibility for the purposes of GCP compliance or pharmacovigilance, detailed descriptions of the investigators roles (eg, safety reporting timelines). The protocol should also define the end of the trial. Pharmacovigilance requirements are now much more strict and the reporting of adverse events should be addressed separately in the protocol, an important part of which is a full list of expected serious adverse events to prevent unnecessary expedited reporting. Guidance on what needs to be included for regulatory compliance in the UK is now available, but the situation in many European countries remains unclear and specific advice should be sought from national authorities.[9] Finally, the protocol should describe the publication plans for the trial, with the intention from the outset that all clinical trial data should be published.

## Selection of patients

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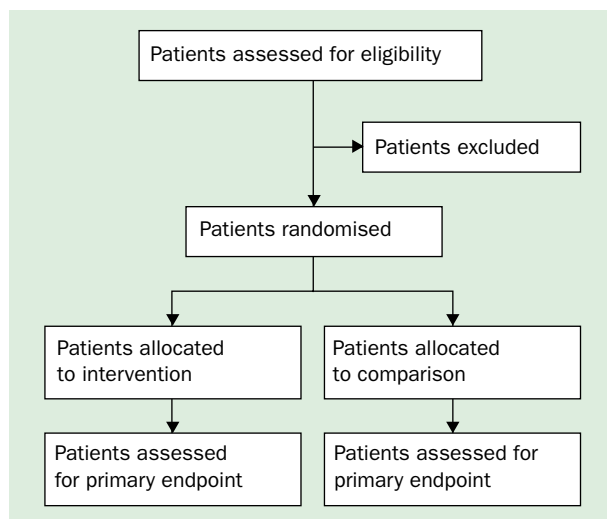
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Well-organised randomised clinical studies commonly change routine treatment of patients with cancer. For example, trials in early breast cancer paved the way from mastectomy to breast-conserving surgery, and many studies established adjuvant systemic treatment for different solid tumours.

A clinical protocol typically has a lengthy (and partly somewhat arbitrary) list of inclusion and exclusion criteria for selection of patients onto a trial. The protocol defines treatment details, leaving little room for free choice, which is viewed as a protocol violation. This policy is scientifically sound because it ensures the accrual of a well-defined set of patients, as well as stringent quality control of trial practice. Although protocol data serve to set standards for later routine clinical practice, future patients treated outside a protocol might not meet the original stringent selection criteria of the reference study (eg, arbitrary age limits or variables of organ function). Mengis and colleagues[10] analysed patients with acute myeloid leukaemia who were treated either within or outside of a clinical phase III protocol. Patients treated outside protocols had a poor outlook, mainly because this group included many elderly patients, or patients with substantial comorbidity who were not eligible for the trials.

The requirement for stringent selection of patients in protocols implies the organisation of many staging procedures before a patient enters the trial. In patients who present with emergency situations (eg, rapidly progressing high-grade lymphoma or small-cell lung cancer with upper vena-cava obstruction), there might not be time to complete all tests required by protocol before treatment must start. Such patients, who are commonly in a poor-risk category because of advanced disease, are excluded from participation in trials and thus do not affect the selected better-risk group who have been accrued.

Assessment of tumour stage depends on the staging procedures available. For example, classification of a tumour as stage III at trial entry will not ensure that patients in the future with stage III tumours will belong to the same risk group because staging procedures can change with the development of new, more refined, diagnostic techniques—so-called stage migration or the Will Rogers phenomenon.[11]

The oncology community therefore faces an important dilemma. Clinical research should meet exacting scientific standards with careful control of experimental conditions. However, when trial data are transferred into routine clinical practice, details of the selection of patients in a reference trial and other rules of the original study will no longer be remembered fully, no matter how appropriate they might have been for the study. Even with stringent selection of patients, substantial heterogeneity among apparently similar patients is still probable.[12] Several large trials have therefore used a so-called open-mind design. The International Adjuvant Lung Cancer Trial[13] allowed the 148 participating centres to define individually the tumour stage to be included in the trial, the dose of cisplatin per cycle, and the choice of an additional drug to help accrual and the generalisation of results. Predictably, this strategy was criticised on the grounds of "heterogeneity of care and centres",[14] but the authors' rebuttal[15] aptly pointed out that the large geographic basis of the study broadens the extent to which the results could be generalised. The same situation applies to the International Collaborative Ovarian Neoplasm (ICON) 3 trial[16] of paclitaxel for first-line treatment of ovarian cancer. Inclusion criteria were deliberately loose (eg, "clinician to be certain that a patient required, and was fit to receive chemotherapy", and "no particular restrictions on the extent of primary surgery"). Advocates of stringent selection of patients for trials criticised this approach,[17] but overlooked the fact that the many patients enrolled onto ICON3 would typically be considered for off-protocol first-line chemotherapy.

What is the solution to these problems? Not a simple one. Stringent selection of patients is mandatory in many phase I and phase II trials, in which detailed questions on antitumour effects, doses of new drugs, and toxic effects must be addressed with great scrutiny. However, in large phase III trials, which are designed to investigate new treatment methods (eg, adjuvant chemotherapy in non-small cell lung cancer) rather than treatment details, the selection of patients should be open-minded or loose. This strategy gives the important advantage that such trials might reflect daily practice better than results from highly selected patients, but at the expense of scientific precision.[12,18]

## Statistical power

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When we embark on a clinical trial, we anticipate that study results will be credible and meaningful; that is they might influence medical practice. If we agree on that idea before

planning a trial, we ought to be aware of where we are going to and how likely it is we will get to the outcome.

If the study treatments are actually different by a given plausible amount (called E), it should be identifiable. Statistical power, usually reported as $1-\beta$, is the ability of the trial to recognise effect E—ie, it tells us the likelihood of achieving a significant result if a true difference as large as E exists between the treatments. By contrast, significance level $\alpha$ is the probability of finding a significant result if there is no difference between treatments. Common values of the level of power and significance are 80% or more and 5% or less, which indicate that in efficacy studies a false-significant result (ie, finding a difference when it does not exist) is a more serious error than a false-negative result (ie, not finding a difference when it does exist). We might change the choices but we cannot elude them; if we want to be less prone to one or both errors we have to increase information and involve more patients.

Intuitively, the larger the effect the more recognisable it is, but how large is a plausible amount? The effect should be both meaningful and achievable and should balance therapeutic advantages and side-effects. Although only modest effects might usually be expected, significant results should be offset against substantial toxic effects.[19] Although the magnitude of such effects are unknown, there is usually enough information about the disease to infer a clinically worthwhile benefit that should be sought. On investigation of who will gain most benefit from therapy, looking for high-risk and responsive patients can increase otherwise limited benefits.[20]

Most cancer trials are based on analysis of time to an event such as overall survival, and sample size is defined mainly with respect to the number of events needed.[21] This number of events ultimately depends on the size of the effect to be recognised, statistical power, and significance level. Not all patients will experience the event thus, once the number of events has been defined, the overall number of patients to be recruited is a function of the rate at which the events occur. Accordingly, the duration and feasibility of the trial will depend on the recruitment rate and the duration of accrual and follow-up. Furthermore, sample size should be increased to some extent because of the attrition bias due to non-compliance and patients lost to follow up.

Estimation of trial size is based on assumptions that could turn out to be wrong; however, although imprecise, estimation of sample size before the trial is explicit evidence of what the investigators are looking for, what they thought about the evidence before the trial, and of the expectations of the forthcoming trial.[22] On completion of the trial, any power calculation is irrelevant: we are concerned only with the precision of the observed results, and confidence intervals give all the needed information.[23]

Strategies for calculation of trial size differ according to the type of research domains.[24] Large trials that aim to assess small effects are inadequate and possibly unethical[25] when complex and toxic treatments are tested, or when prognosis is very poor. By contrast, small trials can be inconclusive and therefore unethical.[26] Positive small trials will almost certainly overestimate the treatment difference, and the more probable negative small trials will be published later than the positive

trials, if at all.[27] Moreover, there are concerns about stopping large trials too early:[28] a guarantee of safety is an undeniable right of study participants but early-stopping rules, however statistically correct they can be, should not compromise clinical interpretation of trial results. Furthermore, similar to small positive trials, early interruption of trials will almost certainly exaggerate the estimate of the treatment effect.

Studies should be planned with adequate size to add substantially to existing information about a disease. Choices about treatment should be justified explicitly, weighing effect sizes against expected toxic effects. Furthermore, trials should look for substantial effects on a primary clinical endpoint (ie, survival or quality of life) and not for marginal effects on surrogate outcomes. Better understanding of which patients actually benefit from treatment should be pursued. Confidence intervals should be given more reliance than significance on interpretation of results, and all incoming trials should be registered to limit selective publication.

## Assessment of outcomes

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The assessment and reporting of outcomes in controlled trials are crucial to the interpretation and generalisability of study results. The past decade has seen a change in emphasis from traditional outcomes based on clinical endpoints such as survival, relapse, and toxic effects and on measuring the effects of disease history, interventions (ie, effectiveness) and management, to those rated either by patients or their carers (health-related quality of life), by patients' utility and trade-offs (time trade-off and standard gamble), or economic analysis (cost-benefit and cost minimisation). The emergence of new technologies such as positron-

emission tomography, or the use of biological markers for the tailoring of treatment strategies, has meant that the definition and assessment of outcome measures could be either too specific (or too general), ambiguous, or subject to differential frequency of measurement, thus affecting the interpretation and generalisability of results (see table).

Although traditional outcomes might be well defined, their assessment may still be problematic, especially if assessment by use of a standard-care policy is chosen. For example, recurrence of colonic adenomas during assessment of the effect of aspirin relies on invasive procedures (ie, colonoscopy, sigmoidoscopy), and unassessed primary outcomes have been as high as 19%.[29] In studies of cytotoxic compounds, in which the primary outcome is clinical response, routine radiographic assessment of tumour area or volume is a key part of outcome measurement. If tumour shrinkage is apparent, the first assessment record of tumour decrease is called the response status; a confirmatory scan done not less than 1 month later defines the response category.[30] However, if a confirmatory report is delayed (ie, done 3 months or later), then the true response rate could be underestimated.[31]

Although assessment of time to event (eg, survival, time to local failure, or disease progression) might seem uncomplicated, interpretation and measurement of this outcome can be ambiguous in the presence of competing risks. This situation occurs when one event (such as cardiovascular death) excludes the chance of the event of interest occurring (eg, death from cancer). In some disease sites (eg, in head and neck malignant disease), intercurrent deaths are common because the malignant disease contributes to a high rate of non-cancer deaths (eg, from smoking or alcohol use). Furthermore, in radiotherapy studies where the endpoint is local control, patients might develop distant relapse or might die from other causes before local relapse. Common analyses (incorrectly) classify these events as censored observations, which result in such competing risks (ie, the cause-specific approach) increasing the estimate of those who do not reach the endpoint of interest.[32,33] Statistical methods that use cumulative incidence and conditional failure curves have been developed to account more accurately for such situations and to provide more appropriate estimates of failure probabilities.

Although studies on toxic effects are less common in the phase III setting, they are universally known as measures of secondary outcome in intervention studies. Measurement of toxic effects can be numeric (eg, counts of platelets, white cells, and neutrophils), clinician assessed (eg, neuropathy, infection, or thrombocytopenia), or reported by the patient (eg, itching, depression, tiredness, or diarrhoea). Toxic effects are usually classified into broad categories of severity (eg, according to WHO, Eastern Cooperative Oncology Group, or Radiation Therapy Oncology Group criteria), and comparisons between groups are made from the number of patients with severe adverse toxic effects (usually grade 3 or 4). Difficulties in assessment of toxic effects arise from variability in classification, frequency of reporting, and unclear definitions in measurement (eg, whether a blank on a medical record means no toxic effects). Blood tests taken at scheduled visits give regular information on haematological variables, but other effects, especially late toxic effects from radiotherapy, might cause problems in the interpretation of study results because of differential ascertainment.

Intermediate or surrogate outcomes allow for more rapid assessment of the interventions in question. In some instances, these outcomes are the only practical endpoints to measure disease management, such as assessment of biochemical response when monitoring prostate-specific antigen or of carcinoembryonic antigen in malignant disorders of the liver. Use of an endpoint such as progression-free survival as a surrogate for overall survival is now accepted by regulatory bodies.[34] Although such decisions might hold appeal because the effectiveness of interventions can be assessed more rapidly and because less active agents can be abandoned sooner, a danger of slippage arises. For instance, if progression-free survival is a strong surrogate for overall survival, then its use may be warranted. However, use of progression-free survival, over time, might be replaced by response. Yet the association between response and survival is at best moderate, leading to a danger of recording a poorer measure of the true outcome of interest.[35]

Outcomes rated by patients such as health-related quality of life are, at the very least, secondary endpoints of almost all studies on treatment and need particluar attention in the study protocol. Schedules for the collection of questionnaires, minimisation of missing data, and analyses of repeated measures have received much attention by researchers over the past 30 years from both a methodological and an operational perspective.[36] Studies with endpoints of health-related quality of life generally need only a proportion of the sample sizes needed for the clinical outcomes. The integration of health-related quality of life and toxic effects has provided a powerful tool to combine clinical endpoints and patient-rated outcomes. The Q-TWiST[37] approach compares survival gains with patient utilities (derived from scores of health-related quality of life) and is a mechanism by which the preferences of the patient can be incorporated into treatment choices.

Quality-adjusted survival as an outcome is the crucial quantity to incorporate into models of economic benefit for therapies which might have a major economic burden. Here, other outcomes of interest include resources needed, less tangible costs (eg, effect on relatives of the patient, home visits

### Key issues of outcome assessment in oncology trials

| Outcome | Issues |
|---|---|
| Traditional clinical: survival, progression-free survival, and toxic effects | Blinded assessment, competing risks, and uniform ascertainment |
| Complementary: health-related quality of life, patients' utility, and economic evaluations | Completeness of data, precise definition of endpoints, appropriate collection of resource use |
| Multiple | Consistency of results across the multiple outcomes, statistical issues |
| Molecular markers | Definition of positive signals and patterns, multiplicity, and statistical issues |

by community workers, or social services), and support services. The main focus in such assessments is the cost-benefit ratio, which highlights the need for consistent measurement of both clinical endpoints and health-related quality of life .

Sample sizes for study protocols are usually based on a single outcome. When possible, multiple outcomes should have only a secondary role to a main question of interest. However, they are important aids in assessment of the net clinical benefit of the intervention and enable use of efficient study principles (eg, correctly scheduled, blinded, and consistent assessment) to ensure reliability of outcome measurement and to facilitate interpretation of study results. In situations where multiple outcomes are essential, they should be declared a priori.

However, possible exceptions are in the design and analysis of studies for gene and proteomic markers.[38] In emerging microarray technologies, in which outcomes or surrogates are the activation of gene or protein markers, making precise statements in advance on the intensity and effect of expression can be difficult. Genetic and proteomic expression could be viewed both as biological outcomes and as prognostic factors. Definition of multiple outcomes may be the only sensible approach to describe a molecular mechanism (similar to liver-function tests done in clinical medicine), in which case the same strategies should be used in the assessment of each component. Traditional methods of statistical design might not be directly applicable and challenges exist to integrate these technologies with conventional approaches.[39]

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