

How can we improve clinical trials?

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It is widely understood that drug development in oncology, as elsewhere in medicine, is typically a lengthy and extremely expensive process. Even so, it is also a risky business with only about 8% of the oncology agents that complete phase I testing ultimately achieving licensing.¹ Improved strategies are needed to shorten the time required to identify genuine therapeutic advances and make them available to patients. More reliable prediction of meaningful activity at an intermediate stage and more accurate and comprehensive estimation of likely toxicity in typical clinical use would improve the success rate and reduce the time, effort and cost associated with the development of unsuccessful agents. There are a number of strategies that have been recommended to improve the new agent development process,² and some less obvious ones that I would like to propose (Supplementary table online).

The classic paradigm of cancer drug development is a legacy of the early era of discovery and investigation of empirically identified cytotoxics.³ The first phase II trials were designed for populations with advanced disease expected to have a grim prognosis, and aimed to identify a minimal or modest signal of activity or to minimize exposure to drugs that were generally highly toxic. Although phase II design has evolved to a certain extent, and typically includes sophisticated pharmacodynamic and target effect assessment, most studies still recruit rather selective cohorts of around 40–50 subjects from 1 or 2 major referral centers. These days the governing concern is most often speed.

However, the confidence interval around the observed response rate (or other end point) is likely to be rather large, the applicability to a less selected population is unknown, and potentially critical but uncommon toxicities might not be identified. In many circumstances, for instance, we might consider 20% response or a few months' improvement in progression-free survival (PFS) as clinically promising, but in typical sample sizes, an observed response rate of 20% may really be as little as 7–8% or as

much as 40%. Similarly, a given observed PFS is likely to reflect the random mix of clinical prognostic factors (many not identifiable or measurable) in a small cohort. When data are derived from the patient mix at a major tertiary centre it is even more likely that an apparently promising PFS is not representative of the population at large.

Nowadays, most new agents are not generally cytotoxic and are generally tested in less desperate circumstances. Nonetheless, their toxicity profiles can be unexpected, and a more reliably predictive basis can be imagined for selecting which agents warrant further testing. Sophisticated target validation, pharmacokinetic/pharmacodynamic, and other translational studies amongst a cohort of cases at a major research center will remain important, but—without taking more time overall—a simultaneous larger cohort of less selected patients in typical community oncology settings could be recruited. The larger sample size is needed for typical outcome end points and toxicity only, allowing quick enrolment. Thus, at the end of 5–12 months, a sponsor would have access to ordinary outcome and safety data from an additional 100–250 'real-world' patients, with a far stronger basis for the critical go/no-go decisions that determine whether phase III trials should be done. Where potential predictive phenotyping or biomarkers are involved (see below), these larger sample sizes will also be helpful.

From a sponsor's point of view this strategy might seem attractive, but unrealistic in terms of costs. However, the UK and the US enjoy publicly-funded cancer trial infrastructures that will co-fund this type of work in the interest of helping to shorten the time it takes to make new classes of active agents available to patients. Trial networks could also work with sponsors to qualify/validate new biomarkers, including genomic and proteomic profiling, some of which will prove able to identify potential responding or non-responding cohorts and/or to effectively

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subdivide participants into more homogeneous groups so that trials can be completed with smaller sample sizes. This kind of research effort typically cannot be completed all within the context of a single trial, but must be carried out in a coordinated way across a series of trials, making it difficult and rarely cost effective for any one sponsor to undertake, but a partnership between companies (probably several) and the academically led trial networks could by validating biomarkers facilitate speedier and more accurate agent development.

The greatest impact on outcomes has been from clinical trials that identify effective combinations. This situation is likely to be no less true in this era of targeted therapeutics development. The complexity and redundancy of signaling pathways suggests that there may be few solid tumors as susceptible to inhibition of a single target as CML or GIST;⁴ however, it usually takes years between phase II clinical testing of a new agent in a given cancer and the launching of definitive and practice-changing comparative trials of combinations. To shorten this cycle, the testing of potentially synergistic combinations of targeted agents needs to be initiated much earlier in the development pathway. The genetically manipulated mouse model systems now available could be employed systematically to select rational combinations for phase II testing in parallel to clinical studies of the involved single agent(s). Extensive preclinical testing and corresponding clinical studies of doublets is costly, but is outweighed by the possibility that patients could benefit several years sooner, or (for the sponsor) the additional usage and sales within the patent period.

In addition, going beyond agent development *per se*, clinical trialists could build portfolios of related trials so as to leverage the maximum volume of information obtained. Trials take years from design to reporting, and when successful, the next trials may need to be even larger. We need to aim to answer more than one research question at a time by combining research questions or using factorial designs. For instance, we might answer an important question about minimizing toxicity, inconvenience or cost while simultaneously testing the addition of a novel entity by setting up a 3-arm trial in which a standard therapy is compared to

reduced-intensity standard therapy on the one hand, as well as to standard plus new therapy on the other. Several trials of this general design have been highly successful in the UK. (COIN: <http://www.ctu.mrc.ac.uk/studies/CR.10.asp>; PICCOLO: http://www.leeds.ac.uk/medicine/nyctru/ProjectPage_Piccolo.htm)

There are several arguments for systematic and thoughtful international coordination of academic trial design—including the all-important one of shortening the time to effective clinical use. Usually, for various reasons, knowledge of trials in development in other regions is incomplete and opportunities for coordinating study designs are lost by the time protocols are finalized. Some clinical developments rapidly lead to widespread alterations in standard practice (in developed economies); other standard practices can remain divergent between countries for a period of time. Both circumstances provide a rationale for planning large trial strategy on an international basis to fill in knowledge gaps.

However, the complexity of multinational joint studies is not necessarily required. Valuable complementary or even synergistic research outcomes can be accomplished with careful consultation and planning of separate trials. Unnecessary duplication can be avoided and opportunities recognized where replication is strategically advisable. Research questions, eligibility cohorts and end points can be coordinated. Similar trials that define eligibility or end points in somewhat different ways usually leave extrapolated conclusions as doubtful. Post hoc meta-analysis is not a good substitute for the coordinated planning of joint or complementary trials.

Supplementary information in the form of a table is available on the *Nature Clinical Practice Oncology* website.

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Competing interests

The author declared he has no competing interests.