

Randomized Clinical Trials
Past and Future

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The history of medicine is filled with examples of ineffective and harmful treatments that became established based on the authority of experts and persisted for decades. The introduction of the randomized clinical trial into medicine in the late nineteen forties transformed medicine to a science and was of landmark importance to public health. Most new treatments don't work, in spite of their theoretical promise. Without properly designed and validly analyzed randomized clinical trials, doctors would be confronted with a plethora of useless drugs and their ability to effectively care for their patients would be seriously compromised. Today doctors are mostly not in that position because pharmaceutical companies have generally been required to perform randomized clinical trials for licensing their drugs and because the NIH has been able to fund randomized clinical trials.

In discussing clinical trials it is important to distinguish developmental trials from confirmatory trials. Developmental trials, also called exploratory trials, early phase trials, or proof of concept trials, are the initial trials used to determine the best dose of the drug, the best route and administration schedule, what other drugs it should be given with and the type of patient most likely to benefit from the drug. These trials are used to determine whether the promise of the drug is sufficient to warrant the expense of a definitive confirmatory trial and, if so, to establish the details of how the drug will be administered and the type of patient to be included in the confirmatory trial. Developmental trials in oncology are frequently not randomized clinical trials. Short term endpoints which indicate drug activity but not necessarily patient benefit are used. Great design flexibility is possible and appropriate for these trials and generally no claims of patient benefit should be based on such trials. Most drugs which appear promising in developmental trials in oncology are found to be ineffective in confirmatory trials.

Confirmatory trials, also called phase III or pivotal trials, are generally randomized clinical trials that are focused on reliably answering a single specific pre-defined hypothesis: does the drug, administered in a defined dose/schedule/regimen to a defined target population of patients result in patient benefit compared to a control regimen. The analysis of a confirmatory trial is generally very simple. It is a single comparison of the distributions of outcomes for the entire group of patients randomized to the new treatment to the entire group of patients randomized to the control regimen. No exclusions are permitted because some patients were not adequately treated (the intention to treat principle). The outcome measure should reflect a direct measure of patient benefit or an intermediate endpoint that has been shown in previous studies to be a valid surrogate of treatment benefit. The analysis plan must be constructed so that the chance of a false positive conclusion is limited to a stated level such as 5%. This means, that if there are interim analyses as data accumulates, the chance of a false positive conclusion at any point must not exceed the 5% in total. The two most common abuses of statistics in evaluating treatments are comparing non-randomized groups of patients and performing numerous comparisons till you find one that is "significant" at the 5% level. Such "data dredging" practices are acceptable in exploratory studies, but they should be viewed as "hypothesis generation" that require proper test in a confirmatory clinical trial.

The FDA has played a key role in promoting good confirmatory clinical trials and in ensuring that licensed drugs are safe and effective. The application of the principles I've described is often not clear cut, however. For example, interpretation of whether a biological measurement is a validated surrogate of clinical benefit can be controversial. This was illustrated recently with clinical trials for reducing blood sugar for diabetes and for increasing HDL cholesterol for patients with cardiovascular disease. In oncology, there was a recent controversy concerning whether prolongation of progression-free survival for patients with newly diagnosed metastatic breast cancer constitutes clinical benefit. Regulation by the FDA has played a critical role in assuring that good studies are performed to establish safety and efficacy. A variety of models for effective regulation are possible. On issues involving controversy, for example, the FDA usually seeks input from an advisory committee which they appoint. The committees review studies conducted by sponsors. The types of studies performed are determined in large part based on Guidance documents developed by FDA staff and then published for public comment. This places the FDA in the position of establishing policy as well as interpreting its application to particular applications. An alternative model might be to have some Guidance documents developed in conjunction with external committees appointed by the Institute of Medicine.

Developments in genomics and biotechnology are dramatically changing the nature of drug development, particularly in oncology. Important new reports every month document the genomic heterogeneity of tumors of the same primary site. Most new drug development is based on inhibiting these new targets. Molecularly targeted drugs, are likely to be effective only for patients whose tumors are driven by the de-regulated pathways that are targets of the drugs. Recent studies indicate that this was true, but unrecognized, even for conventional chemotherapy. Drugs like doxorubicin and paclitaxel, though widely used for patients with breast cancer, appear only effective for those women whose tumors have amplification of the HER2 gene or whose tumors do not express estrogen receptors. Large randomized clinical trials involving thousands of patients and a decade of development and conduct were necessary to see the benefit of these drugs because most of the patients treated did not benefit, so the overall average effects were rather small. When randomized clinical trials were performed for evaluating trastuzumab (Herceptin) in patients with axillary node positive breast cancer whose tumors had amplified HER2 genes, however, the improvements in disease free survival were dramatic. Such dramatic improvements in the efficiency and predictive accuracy of clinical trials are possible when eligible patients are selected by a predictive assay for having tumors likely to benefit from the new drug(1-3). This new approach, while preserving the advantages of the randomized clinical trial, not only enables smaller clinical trials to establish drug effectiveness, it would ensure that more of the treated patients actually benefit from the treatment. Currently in oncology, we generally treat many patients for each single patient who benefits. The new approach could also have large benefits on the economics of health care. The majority of patients who are treated for no benefit, would be spared the side-effects as well as expense.

There are major challenges to the translation of genomics and biotechnology to patient benefit. One challenge is the acceptance by industry that developing different drugs for

biologically segmented cancer types is potentially profitable. A second challenge is the need of drug developers to develop a biological assay (test) that identifies the patients who have tumors that are good candidates for the specific drug. The assay must be developed and analytically validated (e.g. reproducibility and robustness) prior to the conduct of the phase III clinical trial. A third challenge is regulatory. The FDA has indicated, for example, that even if a new drug prolongs survival compared to the control regimen in test positive patients, their regulations would not enable them to approve the test unless the new drug was shown to be ineffective for test negative patients. Lack of an approved test would mean that the drug itself would not be available or usable. Conducting adequate randomized clinical trials separately in test negative and in test positive patients, however, may lead to actually slower drug development than in developing the drug in the traditional way without a test. More importantly, however, it is problematic to enter a patient onto a randomized clinical trial in order to show that a drug that you do not believe will work for them actually does not work. It is problematic from the point of view of physician equipoise even though our understanding of molecular targets is often imperfect and sometimes faulty.

This issue of testing drugs in patients for whom they are not expected to work is one example of the regulatory barriers involved in developing new cancer drugs in conjunction with molecular diagnostics that identify which patients whom the drugs actually benefit. Even if both test positive and test negative patients are included in such clinical trials, new paradigms for data analysis need to be considered. FDA insistence on prospective balancing of the randomization by the test result is inhibiting use of new sound and innovative methods. Similarly, new paradigms for use of prospective subset analysis that controls the study-wise false positive rate and for prospectively planned analysis of patient samples from previously conducted clinical trials are needed if we are to deliver the benefits of genomics and biotechnology to patients in a practical time frame(4).

Conclusions

The introduction of the randomized clinical trial transformed medicine into a science and was of landmark importance to public health. Most new treatments don't work, in spite of their theoretical promise. Without properly designed and validly analyzed randomized clinical trials, doctors would be confronted with a plethora of useless drugs and their ability to effectively care for their patients would be seriously compromised.

The FDA has played a key role in promoting good confirmatory clinical trials and in ensuring that licensed drugs are safe and effective. We have good clinical trials in large part because FDA has required them.

Many cancer patients do not benefit from the treatments they take; we often treat the many to benefit the few. Developments in genomics and biotechnology, however, place us on the threshold of a new era of predictive therapeutics in oncology in which we can develop drugs and companion diagnostics to match the right patient with the right

treatment. These developments can have enormous benefits for patients and for the economics of health care.

The development and regulation of drugs and diagnostics are becoming much more complex. This provides many new bottlenecks to licensing and pathways for failure even with effective drugs and valuable diagnostics. New regulatory legislation and new models for development of FDA Guidances may help ensure that efficient regulatory pathways exist for the licensing of effective therapeutics and companion diagnostics.

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