A new type of trial design can help the healthcare industry bring beneficial therapies to patients sooner and stop researching inferior ones earlier.

Value has found a place at the heart of healthcare innovation. For money-conscious governments and other actors in the system, it’s not enough that a new treatment be beneficial and safe. It also needs to be cost effective.

This emphasis on value is even changing the profile of the pharmaceutical workforce. As the Financial Times wrote, “Novartis employs more than 1,200 dual-qualified mathematicians and engineers to analyse big data sets and calculate the value of new drugs – for instance, their potential to reduce hospitalisations and so cut costs. As recently as six years ago, not a single one was on the payroll.”

Research into novel ways to design clinical trials, which I conducted with Martin Forster (University of York, United Kingdom) and Paolo Pertile (University of Verona, Italy), fits in this overall trend towards seeking maximum value. Some of our initial work was recently accepted for publication in the Journal of the Royal Statistical Society – Series B, and we continue to extend our research in value-based adaptive trial design.

Reducing the burden of recruitment

It is challenging and costly to recruit patients to a clinical study. In a conventional trial, investigators first compute how many participants they need to achieve a statistical goal, e.g. a 95 percent confidence interval. The trial can only start once this number of patients – which can be quite large – has been enrolled. It is common for a trial to run into recruitment issues and incur delays, contributing to rising costs.

This has spurred interest in sequential trials, a specific type of adaptive trial design that allows for the gradual enrolment of smaller groups of patients. Instead of waiting for 1,000 patients to be enrolled, for example, the trial can start with, say, 200 patients. Upon seeing the results of this group, investigators can decide whether to enrol the next batch or to stop the trial, thereby managing costs.

Stopping a trial doesn’t necessarily mean that the treatment is unsafe or ineffective. Sometimes it could be that the treatment is extremely successful and should be brought to market early. Either way, it makes sense to optimise the trial length to protect patient safety and maximise benefits to society.

Going a step further, we are proposing a fully sequential trial design that allows for even greater flexibility and faster decisions concerning patient enrolment. It actually eliminates the need to proceed by stages (e.g. to enrol patients one batch at a time) and accounts for the time delays between treatment and observing patient outcomes. With
every data point that comes in – any patient observation, across sites – our model accurately predicts whether it has become cost effective to stop the trial.

Three unique particularities

To our knowledge, our model is the first to combine the following features:

1. It looks jointly at medical effectiveness and cost effectiveness, two aspects that have typically been evaluated separately. It assesses how beneficial the therapy is expected to be, namely in terms of QALY (quality-adjusted life-years). QALY is a very practical measure that answers the question: Does a treatment actually improve a patient’s life? Then this assessment is balanced with the cost of learning about these benefits (i.e. running the trial).

2. It helps to rein in the high costs of clinical trials as it is able to expedite the decision whether to continue or stop a trial. It does that by taking into account every data point (observation) as it comes in. This alleviates concern about unnecessary recruitment to the trial, past the point at which evidence is deemed to be conclusive.

3. It optimises decision making by explicitly accounting for the fact that treatment outcomes are observed with a delay, or to put it another way, data on benefits often accrue over time. For example, stent therapy (to unblock an artery) may be deemed successful based on its mortality rate up to one year later. Investigators don’t know yet what this one-year outcome will be, but they do have an idea based on the patients they’ve seen so far. The model allows them to dynamically project out what the outcome is likely to be, based on incoming (or preliminary) data. Specifically, the model doesn’t just look at one outcome (e.g. mortality); it includes financial outcomes and all health outcomes (e.g. higher quality of life).

Our model applies to two-armed phase III clinical trials in which data on primary outcomes arrive with delay (two-armed means the trial has two groups: one acting as a control, the other receiving the studied treatment). This allows investigators to decide whether to randomise further patients to the two arms even while some patient data are pending. For example, care outcomes might only become available some weeks after the start of treatment. It has been shown to outperform alternative, non-sequential trial designs in terms of the expected benefits of treatment adoption, net of trial costs. Ongoing research extends this work to handle multiple trial arms, learning with more patient characteristics, as well as other practical issues, and is funded in part by a European Union research grant.

Application in the business world

Business executives and project managers constantly need to make decisions concerning scarce resource allocation. When should development of a new product be dropped or expedited? How to weigh the opportunity cost of potentially poor decisions made with too little information?

Bayesian models such as ours can help speed up decision making during product development, in the face of incomplete or trickling-in information. There are ways to balance out the expected future benefits of a new product with its cost of development. All managers want to innovate and develop new products, but they also need to be mindful of budgets.

With the advent of real-time data, aided by new tools such as cloud computing, determining how long to spend learning about a potential new product doesn’t need to be all guesswork. Dynamic data analysis can reduce forecasting uncertainty.

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