Adapt and Update: The Benefits of Bayesian

Dr Yannis Jemiai, Chief Scientific Officer at Cytel, discusses the impact of Bayesian and adaptive clinical trial designs amid COVID-19, and glances to their expanded future adoption post-pandemic

ICT: **How has adaptive clinical trial design developed and progressed in recent years?**

Dr Yannis Jemiai: Adaptive clinical trials have existed for decades, but the complexity of their designs has made them difficult to implement for much of this time. The design and implementation of an adaptive trial involves more than just statistical know-how. Sponsors need skilled statisticians who can also identify when an adaptation will most likely facilitate their goals, whether it be stopping the trial early or ensuring it has adequate power. Moreover, adaptive designs require forecasting technology to determine the best times for interim analyses. Altogether, this means the advent of powerful computing capabilities has been necessary to make adaptive trial designs easier and more accessible to statisticians.

Adaptive designs can now support a number of scientific and regulatory goals. Multi-arm trials, for example, enable dozens of potential new medicines to be tested against a single comparator arm. Meanwhile, multi-stage designs have become more common and sample size re-estimations, which were typically not used just 10 years ago, are now highly familiar to the industry. Finally, the range and variety of trial design is able to meet sponsor needs thanks to accessible technology.

How does Bayesian clinical trial design compare to traditional methods of trial design?

The premise of a Bayesian clinical trial is that this method allows scientists to update their beliefs about a hypothesis as a clinical trial progresses, rather than waiting for a 'big reveal' that might, in fact, demonstrate a failure to show safety or efficacy. There are, therefore, efficiency benefits, which enable unplanned early stops when things go awry, although this is just the beginning.

Due to the fact that Bayesian methods enable beliefs to be updated, historical data can be used to construct what are called 'informed priors', which are essentially the starting point of this process and informed by data already collected. Bayesian methods can also create a strong framework for assessing the risk-benefit profiles of new products. These can also be used for programme- and portfolio-level decision-making across the clinical development journey, and for larger sponsors across the entire portfolio of assets under consideration.

What kind of Bayesian strategies can researchers use to optimise their clinical trials?

Bayesian statistics has close ties to decision theory, which is the mathematical basis of strategic choice. This means Bayesian methods are well placed to support sponsors in their efforts to choose trial designs that optimise their clinical trial. Such methods enable them to quickly consolidate and compare different therapies across trials, and also affords the flexibility to learn and respond to unexpected findings.

Should all trials be adaptive and leverage Bayesian methods?

Not at all. Adaptive designs and Bayesian methods help generate hypotheses and evidence, but within any given context different strategies should be considered. Sometimes a traditional trial design might be best, while at other times, a simpler design may lead to desirable results more quickly. Cytel recently worked with a client seeking to manage enrolment limitations and wanting to use a sample size re-estimation design. Examining the clinical trial design space led to the conclusion that a group sequential design (GSD) actually met the objectives more effectively. GSD designs also enable interim analyses, but are far simpler than many of the currently used adaptive and Bayesian designs.

What sponsors essentially need is a statistician who understands their strategic priorities – maintaining costs or limiting sample sizes, for

example – and has the tools to explore hundreds or thousands of different optimisation options. It is also important to have people who can effectively implement these designs. For example, when designing an adaptive or Bayesian trial, having a knowledgeable data management team equipped to implement the design can make a huge difference, working in tandem with statisticians when needs arise.

We currently see drug developers who are open to using more innovative designs. Do you see such designs phasing out post-pandemic?

Actually, I see the use of these designs increasing post-pandemic. During the height of the pandemic, new information about COVID-19 was constantly and rapidly emerging. It was critical to take advantage of these new insights to inform the best possible route forward for clinical development. Bayesian designs are perfectly suited for such accelerated learning. Additionally, while there has typically been a lot of anxiety around the use of both Bayesian and adaptive designs, the pandemic made the adoption of these necessary, particularly to conclude trials that had already begun.

Bayesian designs require only tweaks to existing statistical models for novel information integration. Traditional, frequentist designs, on the other hand, require rebuilding statistical models from scratch – which is incredibly costly and can halt a trial in its tracks.

Regarding Bayesian designs, regulators have shown they are open to these, and the industry at large has learned a great deal about them this past year. Now sponsors are better situated to understand and take advantage of the immense potential of Bayesian designs.

As for adaptive designs, certain types have become part and parcel of industry culture. For example, the Promising Zone Design has been used fifteen times in the last ten years, and is popular with those trying to manage sample sizes and tailor investment decisions to trial power.

The pandemic has also made other designs, such as basket and umbrella trials, far more familiar to drug developers than they were before. These are difficult to launch without a coordinated effort from governments or foundations, but it will be interesting to see if the private sector is in a position to take these on.

Can you tell us more about adaptive platform trials? What are the benefits to their use, and what are the associated challenges for their implementation?

Platform trials enable researchers to test many different therapies against a single control. This concept leads to many benefits. Fewer patients are enrolled into the control arm of a clinical trial, subsequently leading to more patients being positioned to receive newer medicines. Secondly, in rapidly changing areas of medicine, the standard of care is constantly updating. No one wants to restart a trial with a new control arm; a platform trial means all the protocols and setup are already streamlined so that, should a control change midway through a trial, the ability to update the standard of comparison is much simpler. Finally, there is a lot of discussion within the industry about whether it will be more cost-effective for smaller sponsors to join platform trials that are already being conducted, rather than begin a full trial. Obviously, the sponsor will save on the control arm, though in many instances a larger comparator arm is required, particularly when using frequentist methods. However, there are other costs to consider – operational, design, protocol, services – that might be streamlined and diminished with platform trials. This means, in theory, platform trials might make the playing field more equal, so they are certainly worthy of further exploration.

What developments need to take place (either technologically or regulatorily, etc.) to further aid industry adoption of adaptive and innovative designs?

As I previously mentioned, adaptive and Bayesian designs both take a lot of computing power to explore. People have heard of cloud computing, but not everyone realises that to harness it for the benefit of trial design selection and optimisation requires a significant investment in technology. Three or four years ago, you would have needed around 30 computers to underpin rapid design exploration to get the fast results needed in today's competitive clinical development environment.

Thankfully, technology solutions are now available that allow statistical consultants to work with clinical trial sponsors to design trials swiftly and effectively with operating characteristics that meet their goals. Such solutions don't always need to be purchased outright, either. Sponsors can work with solution providers under the guidance of statisticians, leveraging these technologies to first explore millions of design options and then prioritise the best design for their trial.

From a regulatory perspective, I think people overestimate how critical regulators are about such designs. The FDA, for example, has been encouraging greater use of adaptive designs since at least 2014, and Greg Campbell, a former Director of Biostatistics at the FDA, has said the body is not as averse to Bayesian designs as sponsors seem to think.

Mostly though, the norms and awareness of the industry are changing across the board. Bayesian and adaptive methods promise more flexibility, although they should not be viewed as a generous free for all – an opportunity to use every tactic available to get your drug through regulators. Rather, these are tools to ensure that potential new medicines get the best chance for trial success and do not fail because of an issue that has nothing to do with clinical benefit, like an underpowered trial.

As Chief Scientific Officer at **Cytel**, **Dr Yannis Jemiai** has oversight of the corporate-level scientific agenda, which includes research portfolios in Bayesian, small sample, and other flexible designs, as well as complex, innovative designs, including adaptive trials, master protocols, and multi-arm multi-stage trials. Yannis also has an extensive portfolio of research in adaptive trial design, financial and pharmaceutical strategy, decision theory, and regulatory affairs.

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