Bayesian Methods: Transforming the Future of Clinical Research

Today, a range of Bayesian methods or techniques are being used to drive some of the most important scientific advancements of our age, from novel oncology drugs and pandemic vaccines to medical device innovation. Bayesian methods offer powerful predictive capabilities and evidence-based hypothesis adjustment, leading to de-risked and expedited clinical trials. Yet these techniques are sometimes avoided owing to the computational complexity required for their successful implementation, as well as the need to elicit prior distributions, which can be a point of contention. This paper discusses the benefit of Bayesian methods in early- and late-phase clinical trial design and explores their often-overlooked role in augmenting and optimising frequentist trials.

From Prior to Posterior – the Method that Updates the Evidence

The essence of the Bayesian technique is to develop an informed or non-informed prior for a specific trial outcome and then apply Bayes' rule to update the prior to a posterior as more data are gathered. Crucially, every piece of available data can be applied to create both the prior and subsequent posteriors, allowing for evolving clinical trials that take account of new in-trial insights. As a result, trials become flexible, allowing for near real-time learnings and accelerated decision-making.

Given enough time and data-gathering, evidence will inevitably lead to increasingly accurate inferences – whatever the prior distribution.[1] Crucially, knowledge gathering from interim analyses becomes simpler, enabling trial managers to discern optimal dosing levels, and also stop and refocus trials where efficacy or safety issues emerge.

Where big data meets the need for fast-paced and flexible trials, Bayesian techniques, such as Bayesian dynamic borrowing and Bayesian hierarchical methods, provide the statistical basis to use all available information to drive fast and accurate decisions about the most successful direction for the trial. Bayesian methods are transforming clinical research in every therapeutic area, from oncology and rare diseases, where they protect patients by efficient modelling, to medical device trials where the gains in effectiveness can be quickly calculated using Bayes' rule.

To Choose Bayesian or Frequentist Methods – Is That the Question?

It can be tempting to set Bayesian and frequentist methods against each other in a fight for statistical supremacy. But, in truth, no one method is better than the other. That said, there is usually a clear choice to make for each trial, and it will depend on myriad factors. Fundamentally, the design should demonstrate a thorough understanding of the research question, be aligned with the programme-level strategy, and be positioned to drive rigorous conclusions under resource and time constraints. With a good understanding of both frequentist and Bayesian methodologies, knowledgeable statisticians can choose the method that best meets the objectives of the trial while considering all parameters.

It is important to note that the two methods are not mutually exclusive and that Bayesian methods can often be used to strengthen frequentist trials, not least through the use of historical data. Bayesian predictive probabilities can be used independently, whether the final primary analysis is planned in a Bayesian or frequentist framework. For example, a Direct Monte Carlo (DMC) approach can use Bayesian predictive probabilities of success to help inform decisions for a frequentist trial. In fact, most existing examples of Bayesian methods utilised in late-stage adaptive clinical trials are frequentist trials that have been calibrated to meet classical frequentist type I error rate and power requirements, using Bayesian decision criteria. That being said, early-phase designs have more routinely been designed using a purely Bayesian approach.

The Bayesian approach is certainly the oldest of the two methods, established in the 18th century, yet it was largely unused in clinical trial design until the 1980s. Frequentist methods were by far the preferred method for drug development in the 1960s and 1970s because of the computational complexity required for the implementation of Bayesian methods. Today, the availability of modern computational power allows the wide implementation of Bayesian methods. However, the deep expertise needed to design Bayesian trials is still a hurdle to their adoption.

With the widespread use of frequentist methods, the p-value and the type 1 error rate (significance level) are widely referenced, indicating the probability of false positives. The main differences between the two methods are that, while frequentist approaches calculate the likelihood of the results being seen if the null hypothesis were true, Bayesian approaches define the probability of the treatment effect exceeding a set threshold based on all available data, including in-trial results.

Importantly, frequentist methods are less intuitive. They can rely on data not observed, such as the sampling distribution under the null hypothesis, and can violate the likelihood principle through a dependence on the clinical trial design. (Conversely, Bayesian methods do not always take into account all the features of clinical trial design, which perhaps they should.) The p-value can also be misinterpreted as the probability that the null hypothesis is true, and in many situations, frequentist methods can be less flexible or efficient. However, both techniques have their strengths and weaknesses, depending on the situation.

Boosting Safety and Efficacy in Early-phase Trials

Bayesian methods are commonly applied to early-phase clinical trial designs. Where little is known about the toxicity of a drug and its

effect on the human body, Bayesian methods can be invaluable for interim analyses, using trial data to adjust doses or stop and refocus trials where efficacy is limited, or where there are safety concerns.

Allocating patients to safe and efficacious doses and establishing the maximum tolerated dose (MTD) are important goals in Phase I trials. Bayesian dose-finding techniques such as the continual reassessment method (CRM), the Bayesian logistic regression method (BLRM) and the modified toxicity probability interval (mTPI) are popular methods to increase the probability of finding the MTD.

Bayesian techniques are also frequently used for Phase Ib expansion cohort trials, where further exploration of the MTD and more accurate assessment of the drug activity takes place, including multiple cohort expansion (MUCE) designs in oncology drug development[2]. Multi-arm Phase II trials, with their more adaptive structure, also benefit from the in-trial posterior adjustments that can compare the success probability for each arm. This has led scientists to use Bayesian hierarchical models to assess efficacy in basket trials where therapeutics are being tested against multiple disease indications[3]. Continuous monitoring in single-arm Phase II trials and dose-ranging designs for non-oncology drug development also benefit from the adaptability of Bayesian techniques[3-5]. In fact, the range of Bayesian techniques now driving precision oncology trial design is testament to the power and accuracy of this method[6].

Solving the Predictive Predicament to Accelerate Drug Development

By using Bayesian approaches, external data can be incorporated to augment the trial design. Relevant data are identified from previous or ongoing studies and assessed for exchangeability with data at the aggregated trial level. Bayesian techniques such as commensurate priors, power priors and meta-analytic predictive (MAP) priors are all powerful tools for incorporating historical information.

The MAP approach uses Markov Chain Monte Carlo (MCMC) algorithms to perform random-effect meta-analysis of historical data to derive a prior distribution. This prior distribution is represented by a parametric mixture, determined by using an expectation-maximisation algorithm. A weakly-informative prior component, derived from the previous steps, can further enhance the robustness of the MAP prior, which can then be assessed along with its effective sample size.

In both Bayesian-only and frequentist-Bayesian combined trials, Bayesian model-based meta-analyses can help to select promising candidates for the next stage of clinical development, as well as anticipate the data requirements for latter-stage design. Particularly in oncology, where drug developers are evaluating seamless and adaptive studies, analysis that evolves with the trial is an essential component.

In any drug development programme, the benefit of the therapy must be shown to outweigh the risks, and every piece of data that may influence the benefit-risk balance should be included in the calculation. Bayesian techniques are particularly well suited to this task, as they can integrate myriad sources of data, including historical trial data, into a single benefit-risk calculation to aid better-informed decision-making.

Frequentist methods for borrowing information from historical studies are also widely used, such as propensity score matching and weighting for individual-level patient data, and matching-adjusted indirect comparison (MAIC) for summary-level data. However, the Bayesian interpretation of the process as a probability has its strengths here.

Bayesian techniques are just as valuable to late-phase and post-market trials as they are to early-phase trials, showing their power in shortening trial durations and reducing the cohorts needed to confirm hypotheses. In a case study redesigning the Phase III OSCAR trial for the use of high-frequency oscillation in acute respiratory distress syndrome (ARDS), Bayesian sequential design showed that the trial duration could have been reduced by 15 to 40 weeks and required 231 to 336 fewer patients[7]. Similarly, another trial showed that adrenaline could have been declared as a superior treatment with 30-day survival rates, with 1500 fewer patients using Bayesian trial design[8].

Post-hoc Bayesian analysis also shows considerable benefits. In both of the recent high-profile EOLIA and ANDROMEDA-SHOCK trials, a large clinically important mortality difference was observed, but a p-value less than or equal to 0.5 was not reached[9]. Post-hoc Bayesian analysis helped inform the interpretation of the study beyond the frequentist's binary (positive or negative) delineation[9,10,11].

In the race to get drugs approved and made available to those who need them, shortened trials and smaller cohorts can accelerate patients' access to new therapies, addressing their unmet medical needs and also saving valuable time and money. Interim analysis is critical for optimising late-stage trials, where patient numbers are larger and the stakes are higher.

Futility is inherently a prediction problem that can be resolved using predictive probabilities or p-values. Yet, seeing as only the former takes into account both observed and yet-to-be-observed data, futility (and early stopping more generally) is better addressed by predictive probability than by p-value. Even partial data can be used to drive decisions, and, although not relevant for regulatory submission, it can provide vital context to help de-risk a trial where there are questions around futility or efficacy, especially for trials with long follow-up periods[12].

Using Bayesian Methods to Expedite and De-risk Trials

Driven in no small part by the computing power and technology available to statisticians today, the first tentative calculations of the 18th century have exploded into a range of powerful Bayesian techniques and methods that are changing the way clinical trials are designed and analysed. From early-phase design to late-phase development, Bayesian techniques are expediting and de-risking trials and even augmenting frequentist designs. They deliver the predictive power to enable scientists to draw robust conclusions and adapt trials. Frequentist techniques will always have a place in trial design, but the case for wider adoption of Bayesian methods is strong. With the increasing demands for targeted therapies and the very urgent medical needs caused by rapidly evolving infectious diseases, such as COVID-19, fast learning and flexible trial designs will become ever more important in bringing therapies to market faster and more efficiently.

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Harari has worked in statistics and data analysis since 2007. His experience includes design and analysis of randomized and cluster-randomized clinical trials, Bayesian data analysis, adaptive designs, statistical emulation, and more. As Principal Statistician at Cytel, Harari leads projects in real-world evidence and develops statistical software for Bayesian trial design and analysis as well as for adaptive strategies. Previously, Harari was a postdoctoral fellow at the University of Toronto and Simon Fraser University.

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Prior to joining Cytel in 2013, where he is currently Principal Statistician and Strategic Consultant, Vlachos was a statistician at Merck Serono and a Professor at Carnegie Mellon University for over twelve years. His research interests lie in adaptive designs, mainly from a Bayesian perspective, as well as hierarchical model testing and checking. However, his secret passion is Text Mining. He has served as Managing Editor of the journal "Bayesian Analysis" as well as on the editorial boards of several other journals and online statistical data and software archives.

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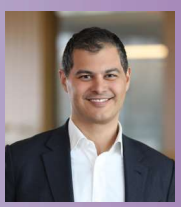

As Chief Scientific Officer at Cytel, Jemiai has oversight of the corporate-level scientific agenda, which includes research portfolios in Bayesian, small sample, and other flexible designs, as well as complex innovative designs, including adaptive trials, master protocols and multi-arm multi-stage (MAMS)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