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Bayesian clinical trials: no more excuses

Biswas *et al*. [1] in their article in this issue, begin their abstract with the statement that 'The Bayesian approach is being increasingly used in medical research.' What follows is a recounting of MD Anderson's extensive role in that phenomenon. A decade ago investigators were reluctant to propose a Bayesian Phase II design to NCI or FDA. Phase I studies based on the continual reassessment method, Bayesian in everything but name, had only begun to be applied in practice. The MD Anderson group has done much to change that, and have not suffered adverse consequences from trail blazing; their reputation has been burnished through these efforts. The authors conclude that it is possible for a biostatistics group in an academic cancer center to apply Bayesian methods on a broad scale and have them accepted by participating investigators, patients, sponsors, and regulatory bodies.

Johnson and Cook [2] use a similar opening line in their article. Their work is about the mostly ignored effect of the use of posterior intervals and the choice of prior on stopping boundaries. The authors, also from MD Anderson, have made Bayesian trial design both a matter of clinical research practice and a methodological focus.

The empirical evidence presented in the work of Berry and colleagues is impressive. A careful review of nearly a thousand online protocols over 5 years reveals that 20% of them had Bayesian aspects. In Phase I and II trials the 'penetrance' increased to 34%. It does not come as a surprise that Phase I and II studies use Bayesian ideas more often than other trials. These studies are inherently sequential and adaptive, particular strengths of the Bayesian approach; in a Phase I study the decision to change the dose should depend on all the information observed so far. In a Phase II study there are compelling reasons to stop the trial early if the agent is ineffective. While we have no data on previous periods, it likely that these proportions were negligible in the 1990s. We certainly have come a long way.

In addition to empirical findings, the article contains case studies chosen to highlight situations where a Bayesian approach can be particularly useful. One case is an unplanned interim analysis, a nightmare for the frequentist approach but not a particularly difficult problem for Bayesians. The second case involves adaptive randomization and the third case is a Phase I/II study. These case studies give us a feel for what it takes to implement these methods into clinical research practice.

In their search, the authors found only seven Bayesian trials designed by a statistician who is not at MD Anderson. While there are certainly some at other centers, the bulk of applied Bayesian clinical trial design in this country is largely confined to a single zip code. Why is this the case? The barriers to entry are many, but three stand out: prior, software, and motivation, a trifecta that we can call PSM.

As Berry and colleagues state, we are all Bayesian at the design stage. A frequentist design requires a prior too, except that it is not a complete distribution but one or two central features. It is essential for the statistician to understand where the parameter value representing the alternative hypothesis comes from, which is certainly a good start for choosing a prior. It is equally essential to admit that this putative value, the dominant determinant of the trial size, is mostly a subjective choice. The authors point to the collaborative efforts that goes into prior selection: identifying relevant literature, reviewing the nature and quality of the historical information, and formulating the prior density. In my experience a good deal of literature search is needed for any sample size calculation and the process of prior selection itself is no more intimidating than the status quo, if the latter is done right. In addition, the Bayesian design toolkit has given us various methods of simulation-based sensitivity analyses to fine-tune the prior, enabling us to filter out priors that may generate unreasonable actions. Nevertheless, choosing a prior can be an uncomfortable affair. Increased exposure and hands-on experience is probably the only way to overcome the P barrier of PSM.

Accessible software is a requirement for any practicing biostatistician. It is unrealistic to write code for the design of each protocol and we gravitate to designs implemented in user-friendly, portable software. The MD Anderson group has made available several programs and it would take a separate article to document and describe the most commonly used ones.

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The biggest impediment, it seems, is the M, or rather, lack of it. Most statisticians have minimal or no exposure to Bayesian methods and standard designs offer the path of least resistance. The system does not reward us for trying new designs, unless we make them an area of methodological research. (Many of the statisticians at MD Anderson have done exactly that, as evidenced by Johnson's article in this issue.) There can be positive feedback here – increased motivation can raise the willingness to elicit priors and invest in software; at the same time, increased exposure to methodology and availability of software will certainly provide more motivation.

Why is this article important? It presents empirical evidence on how common Bayesian designs have become at MD Anderson. More so, it provides a peek behind the curtain, giving us an idea about what it takes to successfully design Bayesian trials and make them part of the clinical research culture at a major academic center. I hope and trust that the examples, methods and software coming out of MD Anderson will help eliminate excuses that biostatisticians around the world have been using to avoid plunging into Bayesian waters.

References

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2. **Johnson V, Cook J.** Bayesian design of single-arm phase II clinical trials with continuous monitoring. *Clin Trials* 2009; **6**: 217–26.

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