Adaptive Clinical Trials' Bayesian Design

Subjects: Others

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Adaptive designs are attracting a keen interest in several disciplines, from a theoretical viewpoint and also potentially from a practical one, and Bayesian adaptive designs, in particular, have raised high expectations in clinical trials.

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1. Introduction

This entry is a bird's eye view of the recent literature on adaptive designs of clinical trials from a Bayesian perspective. Statistics plays a prominent role in the design as well as the analysis of the results of a clinical study, and Bayesian ideas are well received by clinicians. In their book, Spiegelhalter and his coauthors [1] make a strong case in favour of Bayesian methods in health care, and in the last two decades Bayesian statistics has had a large impact in the medical field (see the superb review by Ashby [2]), the more so as its implementation gets easier thanks to better computational facilities. "Bayesian clinical trials: no more excuses" is the title of an editorial in Vol 6(3) of Clinical Trials [3]. The Bayesian approach has a good reputation for producing scientific openness and honesty.

The Bayesian paradigm is especially appropriate at the planning stage of a clinical trial, when external information, such as historical data, findings from previous studies, and expert opinions, is often available and awaiting to be made the most of. As Donald Berry and his colleagues state in [4], we are all Bayesian at the design stage! Health authorities have issued important statements on the statistical, clinical and regulatory aspects of Bayesian clinical trials [5][6], recently allowing and even advocating the use of innovative methods, in particular adaptive design; as the editors of this Special Issue point out, most statistical and biomedical journals have recently hosted proposals of trial designs with a Bayesian slant, in some cases virtual re-executions of published trials. A search carried out in PubMed in August 2020 has returned nearly 300 publications (half of them published in the last decade) which either propose or use Bayesian adaptive methods in the design of a clinical trial. This may be also thanks to the popularization by Donald Berry [7][8][9][10][11] and the efforts made by statisticians working in the pharmaceutical industry, one of the main players in the design of clinical trials, to incorporate Bayesian methods. This is shown in leading journals in clinical trial methodology, like Pharmaceutical Statistics, The Journal of Biopharmaceutical Statistics or Biometrical Journal.

Some confusion occasionally arises between the concepts of "Bayesian" and of "adaptive" design, because of similarities in the outlook: in the Bayesian paradigm, accrued data are used to update the prior distribution on the

parameters, via Bayes' Theorem, and in response-adaptive experiments the accrued data are used at each step, namely after each observation or predefined group of observations, to update the next planning decision. Either approach (Bayesian or adaptive) can stand on its own, and has developed independently of the other: we clarify this point later.

We are interested in trial designs that are both Bayesian and adaptive. The data are recursively evaluated during the experiment: the posterior parameter distribution is recursively updated and used to modify the execution of the trial according to a previously established rule. The textbook by Berry, Carlin, Lee, and Muller [12] successfully illustrates Bayesian adaptive methods in clinical research and deals with design issues too. It goes almost without saying that randomization is a must in a clinical trial (for Bayesians too), to counteract several types of bias, for instance selection bias.

2. Bayesian Adaptive Designs in Registered Trials

Adaptive designs are mathematically sophisticated instruments. Their development is fairly recent, and the split that can be observed between theory and practice is not at all surprising. There are several obstacles—both technical and practical—to launching an adaptive trial, beyond the significant time and effort required by any clinical trial. Among other things, adaptive design requires updating information on accrued data, the speed of acquisition may be highly variable, so there is the need to identify short-term endpoints that can be used to accurately predict treatment responses such as long-term mortality in terms of a gold-standard endpoint. The steps required to establish this type of design in a novel context are indeed fairly complex, as some case studies show (see for instance Mason et al. [13]). As to the Bayesian approach, this may include specialized software programs to run the study design, only made possible by recent advancements in computational algorithms and computer hardware [14].

Nevertheless, it is worth remarking that the philosophy of Bayesian adaptive designs has already made its way into the clinic. They are now fairly well established in cancer research [10], and to a lesser extent, in other clinical areas. As well as single study designs, Bayesian adaptive methods are being employed to build "platform" designs (Adaptive Platform Trials). These are trials for simultaneous testing of multiple treatment strategies in separate groups, with plans to discontinue any group that is definitively inferior at planned interim analyses. Trial patients are enrolled in a continuous manner via a common master protocol, with interventions entering and leaving the platform on the basis of a predefined decision algorithm. Several Adaptive Platform Trials are now funded in various disease areas (see Angus et al. [15], Brown et al. [16] and Talisa et al. [17] for a discussion).

The following is a non-exhaustive list of recent or still ongoing clinical trials that incorporate Bayesian adaptive design features:

- The Randomized Embedded Multifactorial Adaptive Platform Trial in Community Acquired Pneumonia (REMAP-CAP): see [18]. It has set up a sub-platform called "REMAP−COVID" on which the evaluation of specific treatments for COVID-19 is run.

- Anti-Thrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) (see [19]), similar in purpose to RECAP-COVID.
- GBM AGILE, an adaptive clinical trial to deliver improved treatments for glioblastoma, now open and enrolling patients [20].
- STURDY, a randomized clinical trial of Vitamin D supplement doses for the prevention of falls in older adults [21].
- The SPRINT trial on safety and efficacy of neublastin in painful lumbosacral radiculopathy [22].
- SARC009: A Phase II study in patients with previously treated, high-grade, advanced sarcoma [23].
- The SHINE clinical trial for hyperglycemia in stroke patients [24][25].
- The EPAD project in neurology [26].
- The BATTLE and BATTLE-2 trials for lung cancer [27][28].
- The I-SPY 2 platform for breast cancer chemotherapy [29]; (see also [30][31][32]).
- A study on Lemborexant, for the treatment of insomnia disorder [33].
- A Phase I non-randomized trial of a combination therapy in patients with pancreatic adenocarcinoma [34].
- A first-in-human study of RG7342 for the treatment of schizophrenia in healthy male subjects [35].
- A newly started Phase II trial in Japan for sarcoma ([36]) also shows the utility of a Bayesian adaptive design.
- A Bayesian response-adaptive trial in tuberculosis is the endTB trial [37].
- Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN) was a Bayesian adaptive phase 2 dose-response study to establish whether UK-279,276 improves recovery in acute ischemic stroke. The adaptive design facilitated early termination for futility ([38]).

3. Conclusions

“Bayesian adaptive clinical trials: a dream for statisticians only?” asks Chevret [39]. Clearly, Bayesian adaptive experiments are not easy to design, let alone to implement. For a start, elicitation of a prior is not a simple matter. In clinical trials, it is generally assumed to be based on historical data. In their book [1] Spiegelhalter, Abrams and Myles recommend attempting both an “enthusiastic” and a “skeptical” prior. On the other hand, Bayesian statistics exercises greater appeal than frequentist on most applied researchers, and the same can be said of adaptive design rules. This explains why the presence of Bayesian and adaptive design methods combined has become massive in the biostatistical literature, notwithstanding the fact that adaptive algorithms are more complex than non-adaptive.

It is this author’s opinion that although there is a widespread consensus that the Bayesian and the adaptive approaches to design go very well together, the field is still rather fragmented. The development has taken place in a relatively short time, and Bayesian adaptive designs are still awaiting in-depth investigation. It is a sad state of affairs that in general there is no sounder way to evaluate the performance of Bayesian (and non-Bayesian) designs other than by computer simulations. Often the simulation scenarios are chosen on the basis of the researchers’ personal preferences, so the conclusions may be debatable.

The book by Yin [40] is a thorough presentation of both Bayesian and frequentist adaptive methods in clinical trial design, but the two approaches are based on fundamentally different paradigms and a comparison of Bayesian

and non-Bayesian designs is possible only in restricted cases. As an example, when several experimental treatments are available for testing, Wason and Trippa [41] compare Bayesian adaptive randomization, which allocates a greater proportion of future patients to treatments that have performed well, to multi-arm multi-stage designs, which use pre-specified stopping boundaries to determine whether experimental treatments should be dropped. The authors show that in this case both are efficient, but neither is superior: it depends on the true state of nature.

In conclusion, it is worth quoting the words of Stallard et al. [42]: “Bayesian adaptive methods are often more bespoke than frequentist approaches… They require more design work than the use of a more standard frequentist method, but can be advantageous in that design choices and their consequences are considered carefully”.

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