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A quick guide why not to use A+B designs

Adaptive Designs Working Group of the MRC Network of Hubs for Trials Methodology Research

This document summarises the main arguments why 3+3 and similar rule-based A+B designs [18,26] are inappropriate for phase I dose escalation studies. These designs are still widely used [17,23-25] although superior model-based designs such as the continual reassessment method (CRM) [9,21] are available.
Besides investigating a toxicity endpoint for one single drug, extensions to model-based designs for other practically relevant settings exist: e.g., two-drug combination therapies [6,11,13,14,32,33], seamless phase I/II designs that assess toxicity and efficacy together [2,4,28,31], and censored time-to-event endpoints (TITE-CRM) [10].

Why model-based[1] designs are preferable to rule-based[2] designs:

- The goal of an early-phase dose escalation study with cytotoxic oncology drugs is to estimate the maximum tolerated dose (MTD) i.e., the highest dose that "does not cause unacceptable side effects" [20], or more statistically speaking, the dose where the probability of dose-limiting toxicities (DLTs) is equal to some prespecified target level, typically between 0.25 and 0.33. Using model-based designs, the MTD at the end of the trial relates to a target probability of DLT that is specified before the trial begins. However, this is not the case with rule-based designs, and the expected probability of DLT at the MTD can vary greatly [7,15].
- More patients receive doses near the MTD with model-based than with A+B designs, where patients are more likely to be overdosed or treated at subtherapeutic doses [1].
- For instance, it was shown in simulations that only about 35% of patients are treated at the optimal dose with a 3+3 design compared to 55% for Bayesian adaptive designs [1].
- Model-based designs allow estimation of the MTD together with an informative measure of precision. However, under a 3+3 design there is a lot of uncertainty around the MTD selected at the end of a trial; the 95% confidence interval for the probability of DLT is either (0.004, 0.64) (for 1 in 6 DLTs) or (0, 0.71) (for 0 in 3 DLTs); if dose de-escalation is allowed in the design, it can also be (0, 0.46) (for 0 in 6 DLTs).
- A+B designs are commonly viewed as simple and straightforward, in opposition to the purported "black box" of model-based designs (where clinicians may feel they are not in control of their study), but there are user-friendly software tools (see below) to facilitate their implementation. Moreover, it is easy to make the "black box" transparent using the concept of "dose transition pathways" [30] that can help understand possible courses of action in a trial that uses a model-based design.

[1] There are model-free (or curve-free) designs that are recommendable, too, but these are not based on simplistic "rules" like A+B and related designs.
[2] Obviously model-based designs also involve certain "rules" e.g., how to update the model. We use the term rule-based here for A+B and related designs. Rule-based designs are also called algorithm-based designs.

- A+B designs are “memoryless” [22] and therefore inefficient: they only use the information from the last cohort of patients that entered the study to determine the next dose whereas model-based designs make use of all data accumulated.
- Although there are some extensions of rule-based designs (e.g., to drug combinations [5,12,16]), they also suffer from the same drawbacks as simple A+B designs, whereas model-based approaches are clearly more flexible and supersede rule-based designs also for more complex questions e.g., when assessing drug combinations [6,11,13,14,32,33] or toxicity together with efficacy [2,4,28,31].
- Where the goal of the dose escalation study is to understand a dose-response relationship (e.g., when looking into a pharmacodynamic marker and not just toxicity), only a model-based approach will be expedient, whereas A+B designs do not adequately characterise the dose-response curve and are therefore useless.

Table 1: Summary of some key features of rule-based and model-based designs.

	Rule-based designs	**Model-based designs**
Target DLT rate	unclear	clearly defined and can be flexibly chosen
Patients treated at the optimal dose	(relatively) few	(relatively) many
Patients treated at subtherapeutic doses	(relatively) many	(relatively) few
Utilisation of available data	poor	efficient
Extension to more complex questions	difficult & dubious	smooth & straightforward
Deviations from the plan (e.g., other doses, different number of patients on a dose)	hard or impossible to incorporate	easily accommodated

Whatever design is used, the model should be viewed as a guiding tool as there are a lot of factors not captured by only looking at DLTs. It provides recommendations for dose-escalation decisions, which can be combined with clinical expertise in order to reach a consensus about what the next cohort of patients will receive.

Some useful (and free) software tools:

- Properties of rule-based A+B designs can be calculated and visualised with this web app: https://graham-wheeler.shinyapps.io/AplusB/.
- CRM designs are easily calculated with the `R` packages `bcrm` [27], `CRM` [19], or `dfcrm` [8].
- Dual agent and multiple endpoints designs are included in the `R` package `crmPack` [3].
- The MD Anderson Cancer Center offers a software library (https://biostatistics.mdanderson.org/softwaredownload) with multiple tools for dose

escalation studies, specifically bCRM, BMA CRM, BOIN Design Desktop Program, CRM, EffTox, Dose Schedule Finder, ToxFinder, UAROET, and U2OET.

- A web-based dose-finding tool `NextGen-DF` [29] is available at http://www.compgenome.org/NGDF.
- The Center for Quantitative Sciences at Vanderbilt University's School of Medicine developed a web app to compare and select among different designs for dose escalation: https://cqs.mc.vanderbilt.edu/shiny/AdaptiveDesignS.

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