Intensive Care Med (2019) 45:668–670
https://doi.org/10.1007/s00134-018-5364-9

WHAT'S NEW IN INTENSIVE CARE

Intensive care medicine in 2050: clinical trials designs

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Background

For a long time, clinical trials have been designed in a fairly standard way. In phase III randomized clinical trials (RCTs), widely considered the top of the evidence pyramid, each patient typically has a 1:1 chance of being allocated to the experimental or the control treatment. The scheme involves a large number of patients, often due to the modest expected benefits, the so-called "effect size". Such a factor has the greatest impact on both sample size and power computations, and it has been reported to explain the failure of most RCTs in critical care medicine where the desired effect size (10.1% on average) is often largely above the observed one (1.4% on average [1]). Even large sample sizes are no guarantee of positive findings, with small observed benefits possibly explained by several problems, such as protocol deviations or unscheduled crossovers diluting treatment effects [2] as well as true negative findings. In addition, the large sample sizes required in RCTs may limit their feasibility due to excessive cost and/or time. Effectiveness of clinical trials might be improved by adopting a more integrated approach which increases flexibility and maximizes the use of accumulated knowledge to reduce sample sizes and to increase effect sizes for selected patient subpopulations.

Using supplementary evidence

Merging the strength of RCTs that are conducted on homogeneous populations and observational studies, where less homogeneous samples are used, appears promising. In this regard, trials that prospectively integrate both RCT and real-world data would be of interest. As an example, the "mixed randomized trial" [3] has been proposed to meet the evolving demands of regulators faster than multiple separate phase III/IV individual trials. This combined approach first randomizes patients to RCT, pragmatic trial, or observational study, then to treatment groups either randomly (for the first two arms) or as per local clinical practice (for the latter arm). Though promising, this new multi-tiered trial design requires thoughtful planning and further validation.

In the ICU, the complexity of critical illness syndromes is a fundamental justification for the adoption of a personalized approach to research [4]. Thus, identifying effectively patients who will benefit from treatment by refining critical illness types has been the motivation for innovative proposals of the so-called "precision medicine", which aims to tailor the treatments given to patients according to their characteristics. This change of paradigm has been mostly beneficial in the oncology setting, where widespread changes in clinical practice for diagnosis and treatment have been increasingly based on genomic features [5]. A number of Phase II and Phase III clinical trial designs have been proposed to test the effectiveness of a biomarker-guided approach to treatment. Pivotal clinical trials of such therapies are based on innovative adaptive and non-adaptive designs.

Innovative designs

Non-adaptive designs

In oncology, biomarker strategy designs allocate patients with certain histological features ("umbrella" trials) or certain specific genomic alterations ("basket" trials) to targeted treatments according to the value of the genetic features or, more generally, biomarkers [6]. While umbrella trials allocate patients to many different treatment arms based on their specific biomarker, in contrast, basket trials test the effect of one drug on a single predictive biomarker in a variety of tumour types. In the light

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of what has been done in oncology, precise information about ICU subsets could lead to targeted treatments or interventions in pre-specified subpopulations that could be assessed similarly.

Adaptive designs

Compared to standard designs, adaptive designs can make clinical trials more flexible by utilising results accumulating in the trial to modify the trial course in accordance with pre-specified rules, aiming at improving the study power and reducing the sample size and trial cost [7, 8]. Their differences with standard designs can be summarized into two main points.

First, besides stopping the whole trial at an early stage for success or lack of efficacy, like interim analyses of standard designs, adaptations are extended to any points of the design [9]. This can be illustrated in three examples (Fig. 1).

- Enrichment designs: While standard designs enrol a broad range of patients and often run post hoc subset analyses to determine those patients who may benefit from the new treatment, adaptive designs allow the eligibility criteria of the trial to be adaptively updated during the trial, excluding patients who appear unlikely to benefit from the new treatment [10]. They have been proposed for potentially enhancing clinical trials in sepsis [11, 12].
- Multi-arm multi-stage (MAMS) designs: MAMS explore multiple treatments, doses, durations or combinations with options to 'drop losers' or 'select winners' early [13]. They intend to eliminate poorly performing arms at the early stages; only treatments showing a predefined degree of advantage against a control treatment are allowed through to the later stages.
- Outcome-adaptive randomization: While standard designs use a fixed allocation ratio, these designs update random allocation probabilities, so that more patients are allocated to the most promising strategy as evidence accumulates. They remain controversial [14].

Secondly, these changes in the trial design have to be pre-specified at the protocol stage to maintain the validity and integrity of the trial. They are thus different from unplanned ad hoc modifications, a deprecated practice

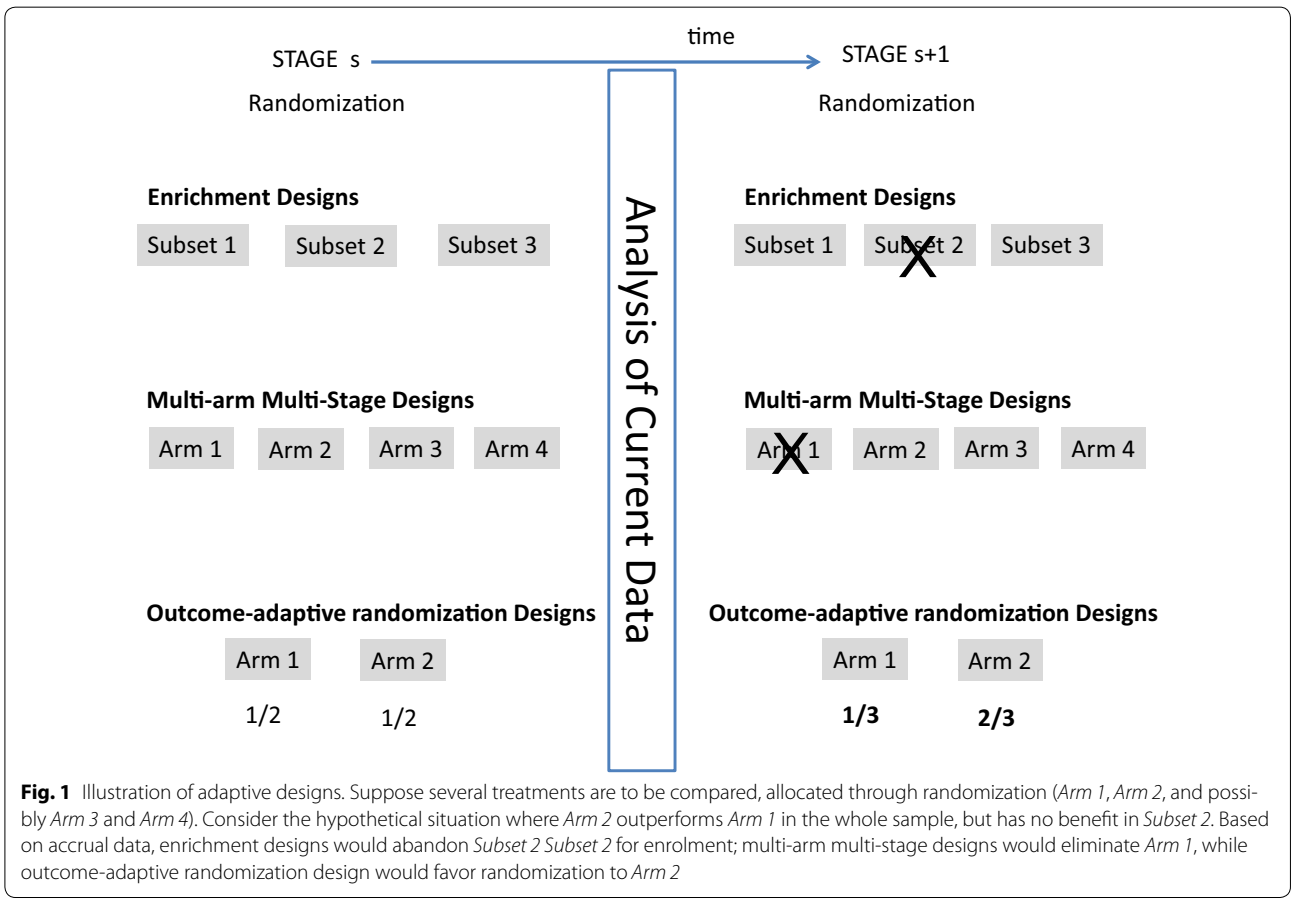

Fig. 1 Illustration of adaptive designs. Suppose several treatments are to be compared, allocated through randomization (*Arm 1*, *Arm 2*, and possibly *Arm 3* and *Arm 4*). Consider the hypothetical situation where *Arm 2* outperforms *Arm 1* in the whole sample, but has no benefit in *Subset 2*. Based on accrual data, enrichment designs would abandon *Subset 2 Subset 2* for enrolment; multi-arm multi-stage designs would eliminate *Arm 1*, while outcome-adaptive randomization design would favor randomization to *Arm 2*

[8]. Adaptive designs either use innovative tests which use more flexible decision rules but still preserve type I errors, or Bayesian inference. In the Bayesian framework, prior information (from previous trials, scientific research or expert opinion) is combined with current information during the trial. There are no traditional hypothesis tests, the concept of type I error adjustment is foreign to this way of thinking, and multiple looks at the data is (statistically) not a problem. Thus, Bayesian statistics and adaptive designs often go hand in hand, and many adaptive designs are currently run in this framework [15].

Conclusions

Originally proposed in oncology to assess many treatments and biomarkers, innovative trial designs have raised many controversial discussions from the beginning, and are still underused and surrounded by misconceptions [8]. Nevertheless, they appear to provide a possible blueprint for therapeutic development in the ICU. Given their significant complexity, multidisciplinary collaborations and team science appear a key to the success of these new design strategies in the ICU.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

Received: 11 July 2018 Accepted: 30 August 2018
Published online: 14 November 2018

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