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Original
Intensive care medicine in 2050: clinical trials designs / Gasparini, M., Chevret, S.. - In: INTENSIVE CARE MEDICINE. - ISSN 0342-4642. - 45:(2019), pp. 668-670. [10.1007/s00134-018-5364-9]

Availability:
This version is available at: 11583/2724788 since: 2019-02-15T12:53:03Z

Publisher:
Springer Verlag

Published
DOI:10.1007/s00134-018-5364-9

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09 November 2026

Intensive Care Medicine in 2050: Clinical trials designs

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Competing interests: none

Word count: 1,000

References: 15

1 table

For a long time, clinical trials have been designed in a fairly standard way. In particular, in confirmatory 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. Such scheme involves a large number of patients, due to the often modest expected benefits ("effect size"), while the statistical requirements to control misconclusions are quite rigid: the type I error rate of false positive findings is consensually fixed at 5% and that of type II error rate of false negative findings fixed at most at 20%. Indeed, the effect size is the factor of greatest impact on both sample size and power computations, which explain the failure of most RCTs in critical care medicine to demonstrate the desired effect size (10.1% on average), often largely above the observed one (1.4% on average, [1]).

If RCT must be characterized ethically by the principle of equipoise, that is, of some genuine uncertainty over whether a treatment will be beneficial, then it has been argued that such negative and likely underpowered trials are unethical [1]: participants may be called to sacrifice their own best interests for the benefit of future patients. Lastly, RCTs are also faced with feasibility issues, when dealing with interventions that could not be easily controlled and quantified such as ICU admission and mechanical ventilatory support.

For all these reasons, it has been claimed that effectiveness of clinical trials should be improved by adopting a more integrated model that increases flexibility and maximizes the use of accumulated knowledge. Novel tools include the smart use of supplementary evidence, adaptive designs, and Bayesian designs.

Using supplementary evidence for precision medicine

First, merging the strength of randomized clinical trials on homogeneous populations (carefully selected through inclusion/exclusion criteria) and observational studies could be promising. In this regard, mixed randomized trials that allocate patients first to trial arm and then to treatment group have been proposed [2]. This solution seems to be mostly applicable to population-based screening or interventions that appear far from the ICU setting.

In the ICU, the complexity of critical illness syndromes is a fundamental justification for the adoption of a personalized approach to research [3]. Thus, identifying more effectively the patients who will benefit from treatment, by refining critical illness

(pheno)types of patients, has been the motivation for innovative proposals of the so-called “precision medicine”. The 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 [4].

To increase our knowledge on the population that should be targeted when designing a particular trial, Bioinformatics and Machine Learning have provided useful tools for the exploration of the huge amount of data derived from new genomic platforms, physiologic waveforms, RCTs and electronic medical records. This was exemplified since the early 2000s with the development of the MIMIC II (Multiparameter Intelligent Monitoring in Intensive Care) databases that contain physiologic signals and vital signs time series captured from ICU patients [5]. To take full advantage of these big data, prediction models should be validated rigorously given their potential to influence decision making [6].

In the light of what has been done in oncology, providing precise information about ICU phenotypes should lead to targeted treatments or interventions in pre-specified subpopulations. Pivotal clinical trials of such therapies will then naturally be based on innovative adaptive and/or Bayesian designs.

Adaptive 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 sample size and trial cost. First proposed in oncology to assess many treatments and biomarkers, they have raised many controversial discussions from the beginning [7], and are still underused [8] and surrounded by misconceptions [9]. Nevertheless, they appear to provide a possible blueprint for therapeutic development in the ICU.

Many innovative adaptive designs have been proposed, including enrichment designs, marker-stratified designs, and marker strategy designs (umbrella trials, basket trials) (Table). Most of these designs aim at treating more patients with more effective treatments, or identifying efficacious drugs for specific subgroups of patients. Such “enrichment” adaptive designs give investigators the ability to study treatment approaches in multiple patient phenotypes within a single trial, while maintaining a reasonable overall sample size, based on their biomarker profiles including omics [10], and shortening the time for drug development. Conversely,

treatments found to be ineffective can be dropped from a study for selected patient subpopulations.

Bayesian designs

Bayesian statistics and adaptive designs go often hand in hand. For instance, taking multiple looks at the data is (statistically) not a problem, since in a Bayesian framework such operation does not have to be adjusted for in any special way. Thus, many adaptive designs have been proposed in this framework. They include Bayesian adaptive biomarker/enrichment designs or randomization-adaptive designs that update random allocation probabilities, so that more patients are allocated to the most promising strategy as evidence accumulate [11].

Bayesian designs can compare multiple active treatment strategies in real-world settings by allowing for the evaluation of more than one new agent at the same time and by dropping/adding arms when a sufficient level of evidence is reached [12]. Such a Multi-Arm Multi-Stage (MAMS) design has been proposed in sepsis-like patients [13].

Conclusions

Adaptive and Bayesian designs are a methodologically sound way to improve clinical trials in critical care but they add significant complexity [14]. First, outcomes should be available soon enough to permit adaptation of the trial design. Furthermore, design is impacted by the accumulated data. This requires statisticians to be engaged both in the planning phase and in the conduct phase of the trial, which may delay its large use in ICU as observed in other settings [15]. However, multidisciplinary collaborations and team science including experts from Genetics, Bioinformatics and Statistics appear a key to the success of these new design strategies in ICU.

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Table: Schematization of proposed biomarker-based adaptive designs

	Enrichment or targeted designs			
Denomination	**Basket trial**	**Umbrella trial**	**Platform trials**	**B**iomarker-based **Bayesian adaptive trial**
Main setting	Single treatment, single biomarker, different subsets of patients	One subset of patients, different biomarkers, Different drugs	Multiple biomarkers and multiple drugs	Response-adaptive randomization
Enrollment	All the subsets are enrolled	One drug for one biomarker (separate enrichment design for each biomarker)	Randomization between strata (allocation probabilities modified to favor assignment of drugs with higher within-stratum response rate)	Modified allocation probabilities within each of biomarker-based treatment
Advantages	Access to targeted agents for patients in various subsets	Conclusions specific to the patient subset	More patients allocated to the best treatment	Incorporate external information, and report based on probabilities on effect size
Drawbacks	Rely on the assumption that profiling based on biomarker is enough	Feasibility, notably for rare diseases (poor accrual and slow trial progress)	Increased samples and heterogeneity	Larger complexity and the involvement of statisticians