Intensive care medicine in 2050: clinical trials designs

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1 table

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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