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The responsibility of undertaking large randomized controlled trials

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The results of the Computerized Glucose Control in Critically Ill Patients (CGAO–Rea) study published in this issue of *Intensive Care Medicine* [1] is an example of what each researcher or clinician should keep in mind to avoid pitfalls at the time of designing an interventional study. The arguments used to formulate the research hypothesis, the experimental design and the conduct of this study all reflect the urgent need to improve our practice of clinical research in the ICU. In the specific area of glucose monitoring and glucose control, there is a clear need for standardization of clinical practice, including definitions, use of standards and reporting of the results. To this end, experts have met twice and recently published recommendations to discuss and—where possible—reach consensus on the most appropriate methods to measure and monitor blood glucose in critically ill patients and on how glycemic control should be assessed

and reported. This group of experts also suggested recommendations on further research and the data needed to reach consensus in the future [2]. Several practical aspects were covered, including “How should we measure and report glucose control when intermittent BG measurements are used?”, “What are the appropriate performance standards for intermittent BG monitors in the ICU?” “Can we use the same measures for assessment of glucose control with continuous and intermittent monitoring?” and “What is acceptable performance for continuous glucose monitoring systems?”.

Following the publication of the results of the NICE–SUGAR (Normoglycaemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation) trial in March 2009 [3], it became clear that the differences in results between the Leuven trials [4, 5] may be related to differences in study design and study conduct; this possibility was further supported with the publication of the Glucontrol [6] and VISEP [7] trials. Differences in glucose target, in glucose monitoring, in hypoglycemia events, in the algorithm used and in the amount and type of nutrition support were all pointed out as possible factors contributing to the differences [8]. It was already evident by the time the results of the NICE–SUGAR trial were presented for the first time that any future study must consider these differences to sort out why the results of the different studies revealed such large discrepancies. CGAO–Rea was launched in October 2009 without any consideration of these arguments.

The risks associated with iatrogenic hypoglycemia induced by tight glucose control were used to boost the development of computerized therapeutic algorithms that had not always been validated in pre-clinical settings. In CGAO–Rea, a study designed to assess the safety and performance of glucose control when using a computer-assisted insulin algorithm, hypoglycemia was considered to be severe only when it was associated with neurological symptoms—in contrast to the definition adopted in

other prospective trials. The use of a standard metrics revealed that even mild and asymptomatic hypoglycemia independently predicted a worsened outcome by different teams [9–11]. The CGAO–Rea study was actually designed to answer two research questions at the same time: (1) does the use of a computerized algorithm improve the quality of glucose control and (2) does tight glycemic control improve the outcome of patients? The answer to the first question is obviously negative, in view of the poor performance of the algorithm demonstrated by the high rate of hypoglycemia, the marginal difference in average blood glucose and the large overlap of blood glucose levels between the two arms of the study. The second question was addressed by a large ambitious multi-centre study using 90-day mortality as the primary outcome variable. Unfortunately, the absence of any difference between groups does not help to solve this issue. Other major limitations and weaknesses of this study include the use of inappropriate glucose meters and the absence of data on nutritional intake, with the latter being a major confounder which explains, at least partially, the divergences in the results of the previous large-scale trials [12].

CGAO–Rea is a reflection of how intensivists can sometimes embark into exciting hypotheses while concomitantly disregarding or even neglecting the available evidence inconsistent with their beliefs [13, 14]. Our urgent needs in the field of glycemic control in the ICU

Table 1 Minimal requirements for an interventional study on glucose control

Data to be reported
Site of sampling (arterial/central venous in patients whose severity of illness justifies an invasive monitoring; capillary acceptable in others)
Blood glucose analyzer used (central lab or blood gas analyzer; meter acceptable only when capillary samples used)
Central tendency, dispersion and hypoglycemia
Nutritional variables (amount of calories provided, route)
Quality and safety issues
Sufficient separation of blood glucose values between experimental arms
Similar rate of hypoglycemia

include validated research tools, such as reliable continuous glucose monitoring and appropriate therapeutic algorithms to assess the hypothesis of improved outcome when severe hyperglycemia, hypoglycemia and high glycemic variability [15] are prevented in carefully designed and well-executed studies meeting the standards of quality and safety discussed among experts (Table 1). To undertake and to perform a large randomized controlled trial is a huge responsibility—towards the scientific community, towards collaborators, nurses and hospitals, and not the least towards patients.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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