

Letter to the Editor

Ethical and methodological considerations on conducting clinical research in poor and low-income countries: Viewpoint of the authors of the BEST TRIP ICP randomized trial in Latin America

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We read with interest the editorial critique of Sahuquillo and Biestro^[10] regarding the BEST TRIP trial,^[2] and appreciate Hunt's editorial response.^[6] However, we believe that the several oversights and misinterpretations that flaw the structure of the editorial, although resolvable by careful reading of the paper, will benefit by clarification by us who were directly involved with the study. Our major concerns are regarding the misrepresentation of the study's focus and the sterile analysis of equipoise.

As stated in the BEST TRIP report, this was not a study of intracranial pressure (ICP) monitoring *per se*. It was designed as an investigation of two protocols of aggressive treatment of intracranial hypertension, one driven by monitored ICP and based on recommendations from the Guidelines for the Management of Acute Brain Injury in Adults^[1] and the other based on current practices at the study (non-monitoring) institutions, which were guided by serial neurological examination and CT imaging. There was no placebo group in this study; both groups were afforded highly aggressive neurological management. As presented in the BEST TRIP report, there was no difference in the incidence of pre-specified clinical neurological deterioration

criteria (one hallmark of inadequate ICP management) between the monitor-driven and the non-monitor-driven protocols. Recognizing the absence of a placebo control group renders specious the suggested parallels between the BEST TRIP trial and ethically questionable studies such as the African zidovudine studies and the Tuskegee and Willowbrook investigations.

From a position of academics in high-income countries (HICs), it is argued that ICP monitoring is the standard of care. However, the guidelines themselves note that the weakness of the literature supporting ICP monitoring reflects the lack of randomized control trial (RCT)-level data. There is no doubt that elevated ICP is a bad prognostic indicator; the evidentiary frisson exists because it has not

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been definitively shown that lowering ICP improves recovery. The correlative nature of the available Class II and III studies cannot differentiate treatment-related selection of patient subgroups with different prognoses versus actually increasing recovery. An objective indication that there is no consensus on ICP monitoring, even in HICs, is the wide variation of its routine use in actual practice (77.4% in the US,^[5] 44.5% in Australia and New Zealand,^[7] 63% in Canada,^[9] and 37% in Europe^[12]). Perhaps naïvely, we believe that these frequencies reflect clinical or global equipoise at HIC centers rather than non-compliance with a true standard of practice.

In low- and middle-income countries (LMICs), although ICP monitoring is generally available (via ventriculostomy), it is rarely used, with availability of neurological surgeons, expense, complications, and labor intensity quoted as reasons. As a result, aggressive treatment of suspected intracranial hypertension is based on serial imaging and neurological examination. The widespread environment of competition for funding and resources in LMICs places the implications of the lack of scientific rigor in a unique context quite different from that in HICs. It is perhaps germane to realize that most, if not all, of the authors of the guidelines have never managed a severe traumatic brain injury (TBI) patient without an ICP monitor.

This brings us to our second major area of concern with the Sahuquillo and Biestro critique, which revolves around the sterility of their analysis of equipoise. As noted in the commentary of Hunt, equipoise may be considered to have superficial and deep aspects. Superficially, it is likely true that our Latin American investigators would have been using ICP monitoring before the trial if it were readily available. Of course, cardiac surgeons would have routinely employed internal mammary artery ligation for angina in the 1950s^[3] and intensivists would have chosen pulmonary artery catheterization for managing critically ill ICU patients four decades later.^[4,8,11] We would all likely benefit from confessing to “medical magpie-ism” and admitting that practice in the high-resource environment of HICs greatly facilitates (and obscures) such a non-scientific proclivity. However, the benefits of living in a high-resource environment also strongly inhibits us from understanding the profoundly different visceral viewpoint that arises from having experienced one’s entire medical career in LMICs. Indeed, the BEST TRIP investigators from the US and Argentina were initially taken aback when the site investigators involved in designing a multicenter prospective observational study suggested that they would be interested in performing an RCT involving ICP-monitor-driven care. Not until after much discussion among ourselves and with our site PIs did we realize that their position of equipoise, although difficult for us initially to understand, was internally valid. Without the indispensable experience that we had gained over a decade of working in Latin America, learning and experiencing their reality, it is quite possible that some

of the BEST TRIP authors might have co-authored the editorial critique of Sahuquillo and Biestro.

It is notable that this trial was evaluated and approved by ethical committees and FWA-approved IRBs in all participating Latin American institutions, as well as by the IRB at the University of Washington in the US. Although there were myriad ethical questions from each entity during these reviews, none found the study unacceptable based on ethical concerns.

As far as conflict of interest is concerned, the site PIs who suggested and performed this study had no interest in its implications in HICs, but were very much interested in finding whether the application of our current ICP-monitor-driven protocols in their environment would warrant the required resources. Although the editorial states that “BEST TRIP is a good example of research that has no practical relevance to the health needs of the host country, but it is apparently important to the foreign sponsors and researchers ...,” we fail to see how demonstrating inadequacies in our use of an important monitoring device is not relevant to the health needs of both the US and Latin American countries involved in the study. We also take issue with their strong implication that this study was influenced by industry. Given the highly limited funding that comes with Fogarty International Center directed/NIH sponsored research awards, there was no way for us to purchase the required monitors. Integra Life Sciences responded positively to our request that they would supply the necessary hardware, despite explicit prohibitions against their having input into the design, execution, analysis, or publication of the study results. This is collaboration, not collusion, and allegations otherwise would benefit from supporting evidence.

In contrast to the implications of the editorial, the BEST TRIP publication explicitly cautions against ready generalization of the results to HIC centers. This is based on the many important differences between these environments and our inability to adequately control for them in our analyses. As the editorial correctly states, the logical next step would be repeating the study at trauma centers in HICs. However, it also posits, “these countries would never allow such a trial to be conducted,” which we believe is incorrect. As noted above, there were sizeable percentages of HIC trauma centers not monitoring prior to the trial, and we perceive an increasing willingness for practitioners who do not routinely monitor to publically admit this following the BEST TRIP publication. A shift in HIC-equipoise balance might not be required to perform such a study.

Finally, our site PIs almost to a person took umbrage at the implication in this editorial that the study ICUs were of limited quality due to lack of resources. Anyone who has spent time in these ICUs will immediately recognize the high level of education, diligence, and

application represented by the involved intensivists, which is clearly reflected in the data presented in the BEST TRIP publication and the online supplement. We offer a standing invitation to Professor Sahuquillo and Dr. Biestro to visit any or all of the BEST TRIP ICUs toward rectifying their difficulty in differentiating resource limitations and quality of care.

We believe that proper response to a careful, thorough reading of the BEST TRIP report is to recognize the critical value of aggressive and attentive management of TBI patients in all settings and to admit that our field's employment of ICP monitoring is under-developed at present, rather than to deny the study's findings. Refinements in threshold setting, TBI subgroup identification, and integration of ICP data with other monitored values and trends appear wanting, but there is no evidence that ICP monitoring should be abandoned.

On the larger stage, it is also important to realize that the medical and ethical literature almost exclusively emanates from academic centers in HICs. The only valid method for assessing the generalizability of this literature to LMICs is to make an unbiased, protracted effort to understand their reality, as perceived by them. In this light, it is notable that none of our Latin American colleagues have ever expressed regret that they suggested this study or participated in its execution.

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Commentary

I read with progressively eager enthusiasm the response of the BESTTRIP authors to the editorial by Drs Sahuquillo and Biestro and my comment on their editorial. It is clear that Chesnut *et al.* of BESTTRIP took aggressive umbrage at their inference that their study was ethically challenged.

Before giving a more specific response to the issue raised by them, I would like to make two points. First, as an early reviewer of the editorial of Sahuquillo *et al.* I apologize that I failed to recognize that an opportunity for acute response by the BESTTRIP authors was not only legitimate but also arguably demanded by the tone of the editorial. I hope to carry out my editorial responsibilities more effectively in the future. Second, their very arthus-like reaction to the editorial demonstrates both the seriousness with which they took their ethical obligations and the importance of addressing

these concerns upfront, as well. As a past chairman of an active bioethics committee, I am gratified by the weight given to these ethical issues, a weight not always in clear evidence, and applaud any opportunity to better discuss the moral underpinnings of any research projects, particularly those with major transcultural or transnational components.

Chesnut's first point is his weakest. To argue that a study group cared for without monitoring does not constitute a "placebo" group, within the common understanding of the phrase, seems disingenuous, if factually accurate. The risk of ethical compromise of the study is not affected by whether or not this is technically a placebo group.

Their subsequent defense is far more persuasive. The lack of clear research or international consensus on the efficacy—regarding outcome—of monitoring is indeed important in the establishment of equipoise.

I would also affirm their point that ventriculostomy, as a diagnostic, and even therapeutic, methodology is inexpensive and virtually universally available. Even the Becker Bolt is remembered by some.

Issues of herd mentality in the understanding of best treatment and the generalizability of data due to cross-cultural distinctions are all also valid attenuators of scientific “certainty.” Ultimately, I believe the expanded defensive arguments of Chesnut *et al.* are fully persuasive.

I eagerly await any continuation of this important conversation with Sahuquillo *et al.* and look forward to their responses. Vigilance in defense of all our patients in the face of any ethical uncertainty is always appropriate, and I applaud both sets of authors for fully engaging in this important conversation.

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