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

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We read with interest the editorial critique of Sahuquillo and Biestro[10] regarding the BEST ' trial,[2] and appreciate Hunt's editorial response.[6] However, we believe that the several over misinterpretations that flaw the structure of the editorial, although resolvable by careful readin

paper, will benefit by clarification by us who were directly involved with the study. Our major 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) monitor was designed as an investigation of two protocols of aggressive treatment of intracranial hyper driven by monitored ICP and based on recommendations from the Guidelines for the Manager Acute Brain Injury in Adults[1] and the other based on current practices at the study (non-mon institutions, which were guided by serial neurological examination and CT imaging. There wa group in this study; both groups were afforded highly aggressive neurological management. A in the BEST TRIP report, there was no difference in the incidence of pre-specified clinical neu deterioration criteria (one hallmark of inadequate ICP management) between the monitor-drive non–monitor-driven protocols. Recognizing the absence of a placebo control group renders spe suggested parallels between the BEST TRIP trial and ethically questionable studies such as the zidovudine studies and the Tuskegee and Willowbrook investigations.

From a position of academics in high-income countries (HICs), it is argued that ICP monitorin standard of care. However, the guidelines themselves note that the weakness of the literature s ICP monitoring reflects the lack of randomized control trial (RCT)-level data. There is no doul elevated ICP is a bad prognostic indicator; the evidentiary frisson exists because it has not bee definitively shown that lowering ICP improves recovery. The correlative nature of the availabl and III studies cannot differentiate treatment-related selection of patient subgroups with differe prognoses versus actually increasing recovery. An objective indication that there is no consens monitoring, even in HICs, is the wide variation of its routine use in actual practice (77.4% in t 44.5% in Australia and New Zealand,[7] 63% in Canada,[9] and 37% in Europe[12]). Perhaps 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 ventriculostomy), it is rarely used, with availability of neurological surgeons, expense, compli labor intensity quoted as reasons. As a result, aggressive treatment of suspected intracranial hy is based on serial imaging and neurological examination. The widespread environment of com funding and resources in LMICs places the implications of the lack of scientific rigor in a uniq quite different from that in HICs. It is perhaps germane to realize that most, if not all, of the au guidelines have never managed a severe traumatic brain injury (TBI) patient without an ICP m

This brings us to our second major area of concern with the Sahuquillo and Biestro critique, w revolves around the sterility of their analysis of equipoise. As noted in the commentary of Hur may be considered to have superficial and deep aspects. Superficially, it is likely true that our American investigators would have been using ICP monitoring before the trial if it were readil Of course, cardiac surgeons would have routinely employed internal mammary artery ligation the 1950s[3] and intensivists would have chosen pulmonary artery catheterization for managin ill ICU patients four decades later.[4,8,11] We would all likely benefit from confessing to “me

magpie-ism" and admitting that practice in the high-resource environment of HICs greatly fac
obscures) such a non-scientific proclivity. However, the benefits of living in a high-resource e
also strongly inhibits us from understanding the profoundly different visceral viewpoint that a
having experienced one's entire medical career in LMICs. Indeed, the BEST TRIP investigato
US and Argentina were initially taken aback when the site investigators involved in designing
multicenter prospective observational study suggested that they would be interested in perfor
involving ICP-monitor-driven care. Not until after much discussion among ourselves and with
did we realize that their position of equipoise, although difficult for us initially to understand,
internally valid. Without the indispensable experience that we had gained over a decade of wo
Latin America, learning and experiencing their reality, it is quite possible that some of the BE
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-approv
all participating Latin American institutions, as well as by the IRB at the University of Washin
US. Although there were myriad ethical questions from each entity during these reviews, none
study unacceptable based on ethical concerns.

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

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

Finally, our site PIs almost to a person took umbrage at the implication in this editorial that the

were of limited quality due to lack of resources. Anyone who has spent time in these ICUs wil immediately recognize the high level of education, diligence, and application represented by tl intensivists, which is clearly reflected in the data presented in the BEST TRIP publication and supplement. We offer a standing invitation to Professor Sahuquillo and Dr. Biestro to visit any BEST TRIP ICUs toward rectifying their difficulty in differentiating resource limitations and c care.

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

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

Footnotes

http://surgicalneurologyint.com/surgicalint_articles/Ethical-and-methodological-considerations-on-conduct research-in-poor-and-low-income-countries:-Viewpoint-of-the-authors-of-the-BEST-TRIP-ICP-randomizec America/

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Commentary

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I read with progressively eager enthusiasm the response of the BESTTRIP authors to the edito Sahuquillo and Biestro and my comment on their editorial. It is clear that Chesnut *et al*. of BE 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 p as an early reviewer of the editorial of Sahuquillo *et al*. I apologize that I failed to recognize th opportunity for acute response by the BESTTRIP authors was not only legitimate but also argu

demanded by the tone of the editorial. I hope to carry out my editorial responsibilities more ef
the future. Second, their very arthus-like reaction to the editorial demonstrates both the serious
which they took their ethical obligations and the importance of addressing these concerns upfr
As a past chairman of an active bioethics committee, I am gratified by the weight given to thes
issues, a weight not always in clear evidence, and applaud any opportunity to better discuss th
underpinnings of any research projects, particularly thosewith major transcultural or transnatic
components.

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

Their subsequent defense is far more persuasive. The lack of clear research or international co
the efficacy–regarding outcome–of monitoring is indeed important in the establishment of equ

I would also affirm their point that ventriculostomy, as a diagnostic, and even therapeutic, met
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
cross-cultural distinctions are all also valid attenuators of scientific “certainty.” Ultimately, I b
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
their responses. Vigilance in defense of all our patients in the face of any ethical uncertainty is
appropriate, and I applaud both sets of authors for fully engaging in this important conversatio

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