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Editorial

Is intracranial pressure monitoring still required in the management of severe traumatic brain injury? Ethical and methodological considerations on conducting clinical research in poor and low-income countries

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Long-term disabilities suffered by patients with severe traumatic brain injury (TBI) are a continuous challenge for health care systems and a burden for patients, their families, and the community in terms of suffering, disability, and monetary cost.[13,19] Approximately 50% of TBI comatose patients with an abnormal computed tomography (CT) scan also have high intracranial pressure (ICP).[22] Death, vegetative state, and severe disability are the expected outcomes in patients with persistent high ICP not controlled by medical and/or surgical treatment. As high ICP cannot be estimated reliably by clinical examination or even sequential imaging, ICP monitoring has been considered a necessary tool for its diagnosis and management.

After decades of ongoing debate about how and when to monitor ICP, a consensus was finally reached in 1995 with the publication of the first evidence-based guidelines (EBGs) for the management of severe TBI in adults, developed under the sponsorship of the Brain Trauma Foundation (BTF).[3] Three consecutive versions of these guidelines have established–as a level II recommendation–that ICP should be monitored in *"all salvageable patients with a severe TBI and an abnormal CT scan"*.[3,30] BTF guidelines are endorsed by most scientific societies worldwide and they have been translated into many languages and disseminated and applied in the United States, Europe, South America, China, and Japan, thus defining the core principles for managing severe TBI. In keeping with the guidelines, care centered on ICP management is the standard for patients with severe TBI in both developed countries and those developing countries that can afford their costly management. A few studies have shown that good adherence to the BTF guidelines improve outcomes and reduce the cost of the acute care.[12,16,24,26]

The recent publication of the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST TRIP) trial in the *New England Journal of Medicine* (NEJM) changed this calm scenario unexpectedly, particularly because some of the investigators coauthoring the paper were also active contributors to recent versions of the BTF guidelines.[7] This randomized clinical trial (RCT), which enrolled 324 patients in 6 hospitals in Bolivia and Ecuador, reported as its main conclusion that ICP-based management increased the 6-month favorable outcome only by a marginal and nonsignificant 5% difference when compared with patients for whom care was guided with serial CTs and clinical examination.[7] Despite some clarifications by the principal investigator,[6] the main

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message conveyed by this trial is that ICP monitoring does not make an outcome difference when managing TBI.[14] Consequently, the debate of whether or not ICP should be monitored has been effectively resuscitated and it is receiving wide media coverage and generating more heat than light among clinicians.[14] Some neurosurgeons and intensivists would even like to have a moratorium until class I evidence is obtained for ICP monitoring.

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 and therefore it provides a good opportunity to raise the issues of double standards, external validity, exploitation of vulnerable populations, the role of personal and clinical equipoise, and the value of biomedical research itself. There is a growing ethical concern for the obvious and hidden risks of conducting certain clinical trials in poor and low-income countries. These trials are frequently funded by pharmaceutical or medical device companies and approved by prestigious regulatory bodies that are based in Western Europe or the United States, countries where some of the trial designs and medical practices employed in these poorer countries would never be permissible.[8]

HOW MUCH EVIDENCE IS SUFFICIENT TO DEFEND, SUPPORT, OR CHANGE CURRENT CLINICAL PRACTICE?

The answer to this question depends on whether a fundamentalist, conservative, or liberal view of the EBM principles is taken.[20] For busy clinicians, EBGs are a convenient way to cope with information overload syndrome, to remain updated in their fields of interest, and to build a common framework for mutual understanding when patients are managed by different specialists.[10] Policy-makers and payers may use some reproducible results to formulate guidelines for implementing legitimate cost-control strategies in a health care scenario with finite resources. However, RCTs–the cornerstone of EBM–were designed to test the effectiveness of new treatments, rather than the accuracy of any diagnostic or monitoring tool, and it is becoming increasingly apparent that extrapolating RCT methodology to the study of these tools is, at the very least, controversial and most likely inappropriate.[27,32] A rigid application of the EBM rules would force us to abandon all monitoring methods, even harmless pulse oximetry, as well as most therapeutic strategies used in neurocritical patients, because no RCT has proven that certain monitoring methods or treatments improve long-term outcome.[1]

While we may remove the few monitors that are being used in low-income countries, we could never do this in developed countries, where any anesthesiologist or intensivist not using, for example, pulse oximetry, may face a malpractice claim should an unexpected adverse event occur, even if no robust evidence exists to show that pulse oximetry positively affects outcome. The BTF guidelines support ICP monitoring in severe TBI, even if the available evidence is less than perfect. In this scenario, is it necessary to raise the evidentiary bar for ICP monitoring? Many of us are satisfied with the level of certainty obtained so far and, as a direct consequence of the BTF's strong commitment to disseminate clinical practice standards, there is lack of clinical equipoise worldwide regarding the need for research on this topic. Most ethical review boards in developed countries would consider it unethical to conduct such a trial.

The wave of discussions generated by the BEST TRIP trial raises legitimate questions about who defines evidence, as well as who benefits from the findings. Why did different stakeholders decide to design and fund this controversial trial? In the case of the sponsoring company, it is obvious that a positive trial would have increased the sales of ICP probes in emerging economies and, therefore, would have increased company profits. However, what were the motives of the National Institutes of Health and the academic investigators for conducting such a trial? Should we accept that their main interest lay only in raising the level of evidence? We strongly see this as a naïve conclusion, which, for many of us, produces a certain amount of skepticism.

In a recent paper discussing who assigns value to the biomedical research enterprise and how that value is assigned, Dresser remarks that lobbying, politics, and commercial interests have too much influence over what is studied and why.[11] Dresser also emphasized that investigator conflicts of interest–whether declared or not–may distort the goals of biomedical research. Most physicians conducting clinical research and participating in research agendas (ourselves included) are employed by institutions where research projects are encouraged. In these institutions, research achievement and scientific output measured by different metrics (i.e., papers published in journals with high impact factors, citations, etc.) are mandatory for academic and clinical promotion, and sometimes help to increase investigator salaries. Participation in a multicenter, multinational RCT is a potential source of research funding in developed countries and sometimes a personal source of income for clinical investigators worldwide, because physicians in many industry-sponsored clinical trials are rewarded financially to enroll patients. Under these circumstances, can physicians maintain their independence and avoid the

conscious or unconscious biases that can seduce them to participate in industry-funded clinical trials?

THE ELASTIC CONCEPT OF CLINICAL EQUIPOISE

Genuine uncertainty regarding the benefit or harm involved in a certain treatment among clinicians or within a community of specialists–in other words, personal and clinical equipoise–is a necessary ethical condition to enroll patients in a RCT in which treatment is selected by chance.[4] Clinical equipoise is a disagreement among the community of expert clinicians and is a much more robust concept than personal or individual equipoise defined as the legitimate, honest certainty, or the lack of it, of the treating physician.[15] When there is a lack of clinical equipoise, is it acceptable to conduct an RCT with practitioners who are in personal equipoise in another country? BEST TRIP's investigators, claimed that "the identification of a group of intensivists in Latin America who managed severe TBI without using available monitors and for whom there was equipoise regarding its efficacy", eliminated this ethical constraint.[6] We consider this statement debatable, to say the least. In a globalized world, in which complex relationships exist between domestic and global research production, clinical equipoise must be also a global concept. What is the reason for conducting a particular clinical trial in a low-income country, when the same trial design is considered unacceptable in a developed country?

Apart from the issue of equipoise, the author's justification might be that, either in Bolivia or Ecuador, patients with a severe TBI would have not received ICP monitoring anyway, so the BEST TRIP investigators were only observing the outcome of patients that had never been monitored in the absence of any clinical trial. The investigators can argue that, as an added value, the patients in the control group received a well-designed, protocol-based management. However, this flawed argument was also used for the justification of a controversial RCT conducted in Africa to test the efficacy of a short-course of zidovudine in hopes of reducing perinatal transmission of human immunodeficiency virus (HIV). This trial raised considerable public awareness and expert concern after its publication in the NEJM.[2,21] The design and implementation of the zidovudine trial (an antiretroviral drug used for the treatment of HIV) has been criticized by many authors with strong scientific and ethical arguments. One of the strongest arguments was raised by Marcia Angell, former editor of the NEJM.[2] The main ethical issue regarding the NIH- and CDC-sponsored short-course zidovudine trial was the fact that 15 of the 16 trials used placebo controls, when long-term zidovudine treatment had been accepted already as the standard of care for HIV-infected pregnant women in the US, and evidence existed that this treatment significantly reduces the birth of children with HIV. The use of placebos would have been denied by any ethical committee if the trial had been conducted in any developed country, but the anticipated benefits of the study caused NIH and CDC officers to consider it ethically acceptable to conduct it in third-world countries. Many have compared this trial to the Tuskeegee trial, in which African American men from rural Alabama were not treated for syphilis–when penicillin was already available–in a study designed to understand the natural evolution of the disease.[2] We face a double-standard scenario when a clinical trial is unacceptable in the sponsor's country but is encouraged and funded in developing countries, where trial costs are at least 50% less, the legislation controlling human research is less strict, and research protocols are seemingly accepted and implemented more easily and more quickly. As Angell remarked, in this setting, neither informed consent nor institutional review approval is a guarantee for patient protection.[2]

In the case of BEST TRIP, randomizing one-half of the patients to a control group without ICP monitoring would not have been approved by any EU country or by the US. As an ethical imperative, research conducted in vulnerable countries and populations must follow the recommendations published by the Council for International Organizations of Medical Sciences (CIOMS), which establishes that participants in clinical research must receive the same protection they would receive in the sponsoring country. CIOMS explicitly states that populations and communities with limited resources participating in clinical research "…are, or may be, vulnerable to exploitation by sponsors and investigators from the relatively wealthy countries and communities".[5,17] An alternative and more ethically robust design for the BEST TRIP trial may have involved some of the US Level I and Level II trauma centers that do not routinely monitor ICP in severe TBI patients.

WE HAVE THE DATA, NOW WHAT? THE NEGLECTED ISSUE OF EXTERNAL VALIDITY

When new data challenging the current clinical standards of the most developed countries have been obtained, even if the ethical approach is questionable, what should be done? Most papers concentrate on evaluating the internal validity to verify that the methodology is sufficiently robust and that systematic bias has been avoided. However, less has been said about the external validity, that is, to what extent the results of a trial can be extrapolated to a population of patients in another setting.[9,25] Concerns about the internal validity of BEST

TRIP have been discussed already by others, and we fully agree with their analysis.[18] However, the extreme health care inequalities between the sponsor and host countries raise serious concerns about this trial's external validity and, therefore, its scientific value. The trial was conducted in Ecuador, a country with a per annum (p.a.) health expenditure per capita (HEPC) of US $616 in 2013, and in Bolivia, with an even lower p.a. HEPC (US $250).[31] The 2013 infant mortality rate (IMR)–the best estimator to reflect the quality of health care–was 18.5 per 1000 live births in Ecuador and 39.8 per 1000 live births in Bolivia, the latter of which is comparable to that in many Sub-Saharan African countries.[23,31]

Can the results of a trial conducted in poor countries be generalized to the US or to any developed country? The US has the highest HEPC in the world–US$ 8608 p.a.–and an IMR of 5.9 per 1000 live births,[31] and mortality for severe TBI is 21% higher in middle- and low-income countries compared with high-income countries.[8] The last figure is based only on those patients who arrive alive to hospital, and does not include the unknown number of victims who experience a TBI but are never admitted to a hospital. To implement complex management schemes, can we generalize data from trials conducted in countries with an inadequate or nonexistent emergency transportation system, where patients are managed in general intensive care units, in trauma centers with limited resources and a staff of doctors trained for a few months only? Can the results be compared with those from patients managed in specialized neurocritical units with high-tech medical equipment? We believe the answer is plain: The only way to determine whether these results can be generalized to different health care settings is to replicate the study in accredited trauma centers–or equivalent settings–in a developed country, although, paradoxically, these countries would never allow such a trial to be conducted.

POTENTIAL SOLUTIONS. THE NEED TO RAISE THE BAR OF INTERNATIONAL ETHICAL STANDARDS

As recently remarked, the health care industry-manufacturers of drugs, devices, and medical equipment and its associated political and lobbying power, heavily influence strategic directions in clinical research. They may intervene, through experts with disclosed or silenced financial industry ties, in clinical guideline formation and dissemination, and may ultimately affect daily clinical practice.[29] The industry's interests are not necessarily aligned with the interests of patients and society[29] and may lead to study participant injury or harm and also reduce the public's trust and confidence in clinical research. So what is the solution to the issues we have raised in this essay? It is obvious that the growing number of clinical trials conducted in vulnerable countries requires commitment from all stakeholders to ensure adherence to a core of internationally accepted ethical principles that reflect one of the basic ethical premises of the Declaration of Helsinki; that is, that the interests of science and society are not an excuse to conduct clinical trials in vulnerable countries. Transnational clinical research should be controlled by internationally accredited ethical review boards, and research protocols rejected in one country should not be given permission to proceed elsewhere.[21] In addition, international human research monitoring agencies should have "…the power to sanction corporations and research groups that fail to respect universal standards".[28]

While these mechanisms are implemented, the role of major journals publishing the results of RCTs is crucial. This is because, as Smith emphasizes, when results are published in a major journal, the study receives "…the journal's stamp of approval", the published results carry a kind of professional approbation, and the paper becomes more attractive to both the readers and media, who may amplify the real value of the results.[28] Traditional peer-review processes used by journal editors to aid in deciding which papers are worth publishing is not capable of filtering some of the more sophisticated techniques of covered marketing and conflicts of interest. The incorporation of ethicists in the peer review process would likely help to raise red flags and to properly consider the routine statement that the study was accepted by the "human review board" of some prestigious university. By rejecting suspicious ethical studies, editors may not be able to help make the world a fairer place, but they will help in building a healthier scientific community and sending a clear message, to both scientists and the industry, that it is unacceptable to exploit and potentially harm a few people for the sake of many.

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Commentary

In "is intracranial pressure monitoring still required…" the authors argue that the provision of "first world" care to only a portion of "third world" patients in a research study is inherently unethical, the results are inapplicable to the "first world," and the treatment violates the equipoise about the treatment by the providers in cases where they have not routinely rendered the available treatments in the past.

Distributive justice, applicability, and equipoise are three of the major girders underlying research ethics, implicitly a reason-based endeavor. The issues that the authors raise are worthy of consideration and careful evaluation.

DISTRIBUTIVE JUSTICE

Distributive justice in a research context is manifested by the idea that the population placed most at risk by an experiment should also be the population that stands to benefit the most from an increase in knowledge.

The authors use the BEST TRIP trial of intracranial pressure monitoring as a springboard to introduce a discussion and indictment of the bioethics of many international trials. Ironically, the two studies that they used to disparage international trials, BEST TRIP and Zidovudine, are both trials which arguably most benefitted the local community by minimizing invasive care. In one case, the equivalent efficacy of a more minimalistic and therefore more affordably available approach, and in the other case the utility of a perinatal medication, which could be easily and inexpensively administered in an epidemic area of human immunodeficiency virus (HIV), were proven not just useful but equivalent to "first world" care. In their targeted recipient populations, the research groups mimic the courage of the North American gay community using itself as test subject in the early HIV trials, and the use at Willowbrook of an extremely at risk population for the evaluation of a Hepatitis vaccination.

In an environment where the availability of what is considered "first world" care is commonly not available, truly informed consent and access to (what is believed to be) an enhancement of the local standard of care may be felt by some to provide adequate moral justification for a research protocol. The clear moral hazard is that this will lead to the provision of deliberately substandard care.

Lifeboat ethics refers to forced choices imposed by limited resources rather than any uncertainty regarding the optimal courses of action in ideal circumstances. Regions where lifeboat ethical constraints are a routine reality present particularly, and dangerously, fraught moral issues in the consideration of any research project or medical treatment. Consider access to limited numbers of ventilators in isolated hospitals, the ethics of the

distribution of organ transplants, and battlefield and flood triage, to name but a few forced choice examples.

The counter argument from realists is that the provision of what may be considered to be a suboptimal level of care is still better than the local standard of care, and that this therefore provides adequate moral justification for such local studies. The idealist argues that this perspective obviously risks, and arguably imposes, the treatment of research subjects as tools rather that individuals, means rather than ends. From either perspective such a double standard is an inherently ethically suspect, if not an ethically taboo action, toward the individual patient.

It must also be remembered that the obligation of the researcher to discover the truth, is distinct from the obligation of the physician to provide what he believes to be the optimal available care. At the same time, it is the physician's role as an agent of the patient which gives the physician the moral standing to treat the patient in the first place, and the role of researcher has no inherent right to either access to, or the trust of, the patient. To the extent that the researcher "hitchhikes" on the privileges assumable by the physician, he is at risk of acting duplicitously, as is the physician who permits this blurring of these distinctions.

This distinction will be revisited in the discussions of equipoise and reason.

APPLICABILITY

The generalizability of research results to a broader population is always an issue in research design, execution, analysis, and discussion. Sample selection and validation prior to the initiation of any study, and *post hoc* analyses of representativeness are legitimately raised by the authors. A full consideration of these issues beyond the scope of this comment. Statistical validation and generalization from a subpopulation is always a difficult issue, particularly insofar as the subpopulation may not be representative of anything but itself. This does not invalidate the results themselves, as long as the tested population is fully and accurately described, but may limit the utility of the results.

EQUIPOISE

The authors define equipoise as "(g) enuine uncertainty regarding the benefit or harm involved in a certain treatment…" Regarding equipoise, the authors argue that clinical equipoise should be global, "among the community of expert clinicians." I would argue that this is impossible, as equipoise can, in the end, only be local, in the senses both that comfort with an evaluation or trial can exist by definition only within a particular circumstance, and by a particular physician/researcher.

Equipoise in this context has two elements, a superficial and a deep.

In the superficial, the argument is implied by the authors that for the specific population of physicians and patients, if the physicians had access to the presumed "superior" treatment for their patients, they would choose it. This is despite the fact that the local physicians stated that they were in equipoise regarding the treatment (potentially suspect, but who is to gainsay). Second, if in fact the physicians were maximizing the care of their local patients by undertaking a lifeboat triage, is this not their role: To maximize their available care to their patients? Better to treat one than none, even if this tilts the scales from the researcher toward the physician. It should not invalidate the results, unless it causes a further sub-selection of the research population.

Finally, we must consider the deep paradox of equipoise. The deep paradox of equipoise in clinical research is its false rationalism. The peculiarity of research, in fact, is that no one will (or should) undertake research without an opinion that they can make things better, in aggregate, for the population or subgroup at issue, and therefore true, knowledge based, equipoise about outcome is impossible regarding the control arm of a study. It is the very uncertainty of this opinion that makes an objective equipoise impossible to establish or implement before the fact. That is, ethical researchers must be of the opinion that what they're offering is, overall, an improvement on the current status quo, particularly for the subgroup studied. The hedge words "opinion," "things," "better," "aggregate," "population," and "subgroup" are all deliberate and open to clarification in any particular circumstance, but belief must tilt the scales of opinion to the performance of the study.

In the end, opinion, upon which equipoise is based, is in turn based on either knowledge or belief or some combination thereof. In the absence of knowledge, which can only be obtained by some proposed study such as a randomized controlled trial (RCT), belief in the efficacy of an untested outcome becomes the only driver of a study, the final arbiter of opinion. Equipoise tips its hat only at its own peril to the understanding that it would be immoral to perform an experiment or piece of research on people unless one expected to improve the overall outcome for humanity or some subgroup thereof. It is also immoral not to do that which, in one's opinion, will be the best thing for the individual patient. Knowledge can only be achieved through experiment. Belief, therefore, must be the basis for experiment, as equipoise requires a balance of opinion, by definition the totals of knowledge and belief, between the arms of a study. Therefore, it is only through belief that one can justify the acquisition of knowledge. Moreover, the more knowledge-based arm of any moral study must always be the control arm, as it constitutes the known. Finally, too strong a belief in the efficacy of a novel therapy should also preclude an RCT as inherently immoral, as it would preclude the provision of the optimal treatment to a portion of the research

population, in the opinion of the clinical researcher. The first users of Penicillin did not withhold the drug awaiting the results of an RCT with satisfactory *P* values. These tensions are irreducible. If progress is to be guided by anything more than closely followed fortuitous accident, belief must trump knowledge, and certainty will always follow behind. Even then, the early follow-up of such a fortuitous accident still requires belief, rather than knowledge.

REASON

In essence then, in a research context, perceived equipoise is the argument that "my belief trumps my knowledge": an unenviable position for a rationalist/scientist to have to take! And I would further argue that it is necessarily the opinion of the individual researcher, rather than some inchoate "community," which ultimately leads that individual to action.

Evidence-based medicine is clearly the ideal circumstance in the abstract. And the authors are indeed correct that much of current medicine is not based in RCTs. And the history of medicine is littered with opinions based on beliefs, which have subsequently been proven wrong as "true" knowledge advanced. But thousands of years of accreted knowledge should not be abandoned, as the inference engine of the human mind routinely judges correctly. And the "true" knowledge accumulated walking the border of moral hazard can also prove incomplete, or flatly wrong. Errors, well intentioned or otherwise, and uncertainties inevitably abound.

It is not clear to me that the authors have fully made their case that the instant discussed research protocols overstepped this moral border, though they make a compelling case that increased scrutiny is critical. But their passionate *cri de coeur* is an important, coherent, and timely warning of the hazards inherent in any incautious research where vulnerable individuals have entrusted their health to others, particularly across wide geographic, cultural, or socioeconomic boundaries.

There is no doubt that this trust has been egregiously violated in the past, and remains at serious risk. In the previously mentioned Willowbrook study of the treatment of hepatitis, direct consent by the population was impossible due to the cognitive compromise of the patient population. Indirect consent might have been acceptable based on their high rates of infection, but deliberate direct exposure of the patients to Hepatitis in the presence of alternative housing was certainly unethical. Also in the U.S., the Tuskegee experiments of observation of patients with untreated syphilis violated any possible ethical physician's norm, when known effective treatment was available. Further, as a prior IRB member and bioethics chairman at a major university medical school, I can attest to the need to restrain and sculpt the enthusiasm of some researchers, and to remind them of their primary clinical obligations, and the need for informed consent as a voluntary contract between partners rather than a technical fig leaf covering undisclosed risks.

The use of untreated control groups in both the instant trials discussed by the authors raises similar questions, though access to a "higher" level of treatment may or may not have been otherwise available to the studied populations. It also emphasizes the extent to which health and public policy are inextricably intertwined, from locally to internationally.

Within the limits of our understanding, in every house where I come I will enter only for the good of my patients, keeping myself far from all intentional ill-doing, is as valid a guiding principle now as it was in the time of Hippocrates, 2400 years ago. Medical research must always be subservient to the obligation to the patient. The authors are to be commended for raising and vigorously exploring these deep and fraught issues.

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