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Was the Gadchiroli trial ethical? Response from the principal investigator

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In 2007, Oxford University Press published a book titled *Ethical issues in international biomedical research: a casebook* edited by James Lavery and others (1). One of the case studies presented by the editors and discussed by two discussants, Zulfiqar Bhutta and Marcia Angell, is titled 'Evaluating home-based treatment strategies for neonatal sepsis in India'. This case study is about the field trial of home-based neonatal care (HBNC) conducted in Gadchiroli, India by us (2). Earlier, Prof Anthony Costello from the Institute of Child Health, London (3) and now Sadath Sayeed from Boston (4) have put forward some facts and arguments about the ethics of the Gadchiroli trial. As the principal investigator of that field trial, I wish to add a few things.

1. In 1993, when we started this trial of HBNC, newborn mortality in developing countries was perceived by global policymakers and international organisations as a hopeless case for which not much could be done. For ethical consolation, most standard guidelines on the care of neonates in the community added the sentence: "If a neonate is sick, immediately hospitalise." Usually nothing more was offered to sick neonates. Because hospitals were neither accessible nor affordable, this advice practically meant: "Let them die." Four million neonates thus died every year, mostly in developing countries, the majority of them without receiving any medical care.

When we realised this cruel reality we were baffled but also compelled to do something for these millions of unreached, uncared for vulnerable neonates. There was little precedent to guide us. The challenge was daunting because standard medical advice was a joke in this situation but anything different would require taking an unchartered, risky path. The choice before us was either let four million neonates continue to die silently, every year, or take a risky path.

2. In 1993, our organisation SEARCH in Gadchiroli district had an ongoing child health programme area and also a non-programme area where only demographic surveillance was

done. The non-programme area represented the situation in rural Maharashtra and was served by the government healthcare services. For the HBNC trial these areas of SEARCH were selected as "intervention" and "control" areas respectively. They were not selected anew for the sake of an experiment. However, the baseline parity of two areas was established by a two-year period of baseline measurement. This has been described clearly in our articles on the HBNC trial (5).

3. The study design thus included an intervention area of 39 villages where a new experimental intervention package, HBNC, was introduced from 1995 onwards in a stepwise manner. It also included a comparison area which we called the "control area" served by the government health system and where the child mortality rates were recorded by our demographic surveillance system. Marcia Angell has criticised this strategy. According to her, we should have introduced state-of-the-art (i.e. the US standard) neonatal care in the control area and compared the efficacy of HBNC against it. What she fails to realise is that health service research is different from a laboratory experiment or a hospital-based clinical trial where the researcher might be able to control most variables in an artificially created experimental situation. Health service research has to be conducted in a real-life situation, and a researcher does not own or control all the health services in the area. Further, what makes her think that it would have been possible to create an island of state-of-the-art medical care in the control area in remote Gadchiroli, 1,000 km from Mumbai, where no doctor wants to go and live?

What then is one expected to do? Should one wait until the best standards, and the resources needed for using them in the control area, are made available, and allow children to die until such time? In a world that hardly cares for the disadvantaged and vulnerable, what would be the ethical obligations of a physician-researcher?

The Helsinki Declaration (6) guides us:

> 17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

Moreover if we had introduced the state-of-the-art newborn care service in the control villages, could we ethically withdraw it after the trial was over? Hence, we limited the HBNC only to the intervention villages. Ethics cannot be made a matter of armchair discourse. It must respond to the situation at the ground.

4. A major question raised by the editors is: "Was it ethically permissible for the investigators not to treat those neonates in the control villages identified with sepsis during the study with effective treatment?"

This criticism is based on incorrect information. We observed neonates only in the 39 intervention villages, and provided them treatment when sepsis was suspected. We did not observe neonates in the control villages for morbidities. This area was a demographic surveillance area wherein we enumerated the population and recorded births and child deaths usually a few weeks to a few months after the event had occurred. Hence no ante-mortem diagnosis of neonatal illnesses was made in the control area. When a child death was reported, the cause of death was assigned by verbal autopsy i.e. retrospective verbal inquiry. This fact has been repeatedly stated very clearly in various articles on the Gadchiroli field trial published in the supplement of the *Journal of Perinatology* (5), including in the diagrams on the study design wherein the observational study was limited only to intervention villages. Thus the criticism is without basis.

5. An important question is: what did we do after the HBNC trial was over? What about post-trial access?

Our approach has been different for the intervention villages, where we directly introduced HBNC, and for the "control" villages where we intervened politically. As an ethical responsibility, we have continued care in these 39 intervention villages until today, 11 years after the original trial was over in 1998. We considered that the situation in the "control" villages represented the situation in the rural areas of Maharashtra state and in India as a whole and it was our responsibility to change it once the HBNC trial had shown that the approach was effective. Hence, for the last 11 years, we have strived to influence policy at the state and national levels to incorporate home-based newborn care in rural areas.

These efforts included, apart from scientific publication and dissemination, an extensive use of action-research, the media, judicial activism and political lobbying. For years we have managed to ensure that child mortality is seen as a major social issue that needs attention in Maharashtra. We conducted a 13-site study to record the level of child mortality in Maharashtra using the same method that we used in our "control" villages. These data provided powerful evidence (7, 8). Debates on the subject were held three times in the state legislature. An official evaluation committee was appointed by the state government, of which I was the chairman, whose reports were submitted to the government and discussed in the legislature. The Mumbai High Court initiated public interest litigation citing our 13-site study report on child mortality in Maharashtra. In this case we presented the evidence on child mortality as well as the possible solution of HBNC as implemented in the Gadchiroli trial. I am glad to write that, partly due to these efforts, the HC ordered the government to introduce the Gadchiroli model of newborn and child care in five districts including all of Gadchiroli (including the "control area" of SEARCH) and the government of Maharashtra made a political commitment in the legislature to introduce community-based newborn and child care in rural and tribal areas of the state. To monitor the progress, we have continued to record births and deaths in the "control area" in Gadchiroli, and we now find that the infant mortality rate has started falling, from the baseline 76/1,000 to 47/1,000 in the last four years. And finally, the 11th Five Year Plan has recommended the introduction of HBNC in nearly 250 districts in India (9). Our interest and efforts did not cease once the trial was over, nor have we disappeared from the area. We continue to live and strive in Gadchiroli.

6. Another of Angell's criticisms concerns the standard of care.

According to her, anything less than (or different from) the internationally accepted standard medical care is unethical. All human beings have a right to receive that standard of care. Now this "standard care" usually means what is accepted in the US or western Europe. Is that necessarily the most desirable medical care? The desirability of a particular medical care is not based only on medical or technological reasons. Other issues, such as its appropriateness, acceptability, feasibility and affordability to people will influence the decision. Obviously in different socio-economic situations and cultures, different models will be more appropriate. These cannot be called sub-standard or "unethical". That position is absurd because it dictates to developing countries that even if they can't eat bread, they must eat cake and only cake. Oral rehydration therapy or community health workers may not be used in developed countries, but they are life-saving solutions for many developing countries.

7. The last question I wish to pose is: Is it ethical to evaluate and pass judgement against any study without completely and carefully studying the available information? The Gadchiroli trial had been extensively reported in 12 research articles published in 2005 in the supplement to the *Journal of Perinatology,* and these have been available on the Internet (10). These articles are not included in the references in the case study in this book published by the editors in 2007. If they had read these, their misconception – that we observed neonates with sepsis in the control area but did not treat them – would have been corrected. Shouldn't they at least verify the facts with the concerned person or organisation (as Zulfiqar Bhutta did by approaching us for certain clarifications) before passing an adverse judgement which reverberates internationally? This is an elementary part of journalistic ethics. Shouldn't the editors of a book on ethics accept this as the minimum standard of ethics?

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Impact of bioethics on patentability of inventions

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Abstract

This paper examines the impact of bioethics on patent claims. The increase in research activities involving human biological materials, and the rush to commercialise inventions derived from such biological materials, can at times result in unethical conduct of research. Questions arise as to whether patent law should concern itself with tainted research that has resulted in an invention or whether it should grant patent rights solely on the basis of the technical improvements resulting from such research. This paper highlights the significance of ethical practice in biomedical research, an issue that may influence the decision to grant patents on inventions. It explores the relation between morality, bioethics and patents from the perspective of the objectives of the patent system and current developments in the law on patents. The inclusion of the morality provision in patent law introduces a mechanism through which inventions derived from tainted research can be filtered at an early stage.

Introduction

The race for patents over inventions derived from human biological materials has given rise to concerns about the private control of human genetic resources. But a far more serious issue has surfaced in the wake of the South Korean stem cell fraud. South Korean scientist Hwang Woo-Suk is said to have coerced his junior colleagues to provide their gametes for stem cell research (1). Hwang fraudulently claimed success in creating human embryonic stem cells through somatic cell nuclear transfer but had inadvertently succeeded in deriving embryonic stem cells from parthenogenesis (1). While the scientist and his group of researchers have had to abandon further research, they have sought patents in various jurisdictions. The grant of a patent to Hwang and his group for this research would enable them to seek royalties and profit from immoral conduct.