EDITORIAL

Response to proposed research to reverse brain death: more than regulatory failure

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In early May 2016, reports of a bizarre study to attempt a reversal of brain death made the headlines (1), but there was not even a squeak from the authorities.

The "Reanima Project" is a collaboration between an Indian surgeon, Himanshu Bansal, and a US-based biotech company, Bioquark Inc. The research will be conducted by Bansal's own biotech company, Revita Life Sciences, at his Anupam hospital in Rudrapur, a city in Uttarakhand state**.**

According to the protocol (ctir.nic.in CTRI/2016/04/006893), researchers will obtain bodies of brain dead patients from other hospitals in the town where this project is situated. These cadavers will be subjected to a "multimodality approach" that includes lasers, neural stimulation, injections of stem cells, peptides and some drugs, over a period of 15 days. The study endpoint is "any evidence of reversal of brain death as noted in clinical examination or EEG."

Revita Life's website (http://revitalife.co.in/) opens with a pop-up message on its latest venture: "Dead man walking: US India project could revive brain dead patients."

This project seems to have received approval from an Institutional Committee for Stem Cell Research set up by the hospital itself. And given the nature of the study, perhaps it is not too surprising that Bansal has ***not*** sought permission from any authorities: such as the Indian Council for Medical Research / Department of Biotechnology (ICMR/DBT)'s National Apex Committee-Stem Cell Research (NAC-SCR); the Health Ministry's Screening Committee (HMSC) that is supposed to screen foreign collaborative research, the Drugs Controller General of India (DCGI), and any independent ethics committee (IEC).

Deafening silence from the authorities

What is more disturbing is the complete and deliberate silence from these authorities even when they know that such an unscientific, unethical and illegal trial is being undertaken in this country. The Medical Council of India has not taken up a *suo moto* case of professional misconduct against the doctor. Neither have professional associations, nor have the courts, nor the national or state human rights councils. One needs an explanation for why all these "leaders of society" would rather turn a blind eye to this outrageous violation of all principles of ethics and science.

For, the project is not scientifically and ethically tenable, and the procedures have no basis in prior research on animals. However, the publicity generated would feed into commonly held superstitions and deceive grieving relatives; and the public would doubt the intentions of other doctors when informed that their loved ones were brain dead, destroying a fragile doctor-patient trust and a fledgling cadaver-based organ transplant programme.

Unscientific and unethical

There is no scientific basis for the notion that someone can be brought back from the dead. The requirement for certification of "brain death" under the Transplantation of Human Organs and Tissues Act, 1994 (THOTA) is that all functions of the brainstem have permanently and irreversible ceased; this certification is made by a team of medical specialists after tests conducted over a period of time (2). Brain death is different from "disorders of consciousness", such as comas which have been reversed in some cases, with varying quality of life after gaining consciousness, or persistent vegetative states**.** This distinction must be emphasised as Bansal and his colleagues have quoted instances of recovery from reversible forms of coma as proof of people recovering from brain death**.**

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In complete contradiction to these facts, the draft informed consent document (ICD) template in the "Reanima Project", obtained from Bioquark, meant to obtain consent from the relative of the brain dead patient and the case report form, imply that there is scientific evidence that brain dead bodies can have residual activity in the brain, and blood circulation that might be revived; that injured tissue could be repaired with stem cells and the other procedures mentioned; and that there are valid techniques for assessing neural repair and neurogenesis in the brain dead. The form also implies that the researcher will have the enormous resources, infrastructure and technically qualified human power to keep blood, liver and kidney function of the brain dead body alive in peak condition for many days, with frequent monitoring – it would have to be more frequent than mentioned in the ICD. There is no evidence of this kind.

Science demands a systematic research process that builds on previous research. Pre-clinical and animal studies to establish proof of principle and safety are necessary before a Phase 1 trial (as this is described on the clinical trials registry) may be carried out on humans. This principle, spelled out in the ICMR's guidelines for biomedical research (3) and in Schedule Y of the Drugs and Cosmetics Act (4), is reiterated in the ICMR-DBT National Guidelines for Stem Cell Research, 2013 (5). Research on stem cells must also be approved by NAC-SCR. The guidelines specify the areas in which stem cell research is permitted, and these do not include research on brain-dead persons. But the National Apex Committee on Stem Cell Research has been silent on this project.

Illegal

Under THOTA, a living person may authorise the removal, to be conducted after he is declared brain dead, of any human organ and /or tissue from his body *for therapeutic use only*. In the case of a person who has already been declared brain dead, the law permits the next of kin to give proxy consent for removal. In neither case does the law allow for research on the body of a person in the event of brain or brainstem death.

The cadaver is to be experimented on for 15 days. What will happen next? As brain death is defined only in THOTA, there is no specific law permitting removal of life support in cases of brain death without organ donation – a flaw recognised in the law - for other reasons. Bansal has said that he will inform families that they must bear the costs after those 15 days. Bansal surely knows that other vital organs of the brain dead patient will stop before the 15 day period. What is the purpose of this misrepresentation? Is he trying to hide his rash actions behind the curtain of hope?

Impact on the organ donation programme

The family of a person declared brain dead is often unable to accept that their loved one is actually dead but on machines that can maintain respiration and circulation for a period. In these circumstances, a project that is premised on the possibility that a person declared brain dead may actually come back to life gives false hope to family members. It can also create doubts in their minds in the physicians' intentions. A doctor's judgement that their relative is brain dead and life support systems should be turned off will be viewed with suspicion. Only families who have refused consent for organ donation will be approached. This will fuel mistrust in the physician's advice and consequently increase suspicion of the cadaver-based organ donation programme.

Preying on desperate hopes

In fact, the impetus behind this study is not science but the conviction held by a few desperate families that the diagnosis of brain death was wrong, and their loved one could be revived. The examples cited by Ira Pastor of Bioquark Inc, the US collaborator, were essentially of disputes between family members and hospital authorities, reported in magazine articles. There is nothing in the indexed scientific literature that justifies conducting this study. Pastor has written in an email that family members of people declared brain dead had "expressed interest in the work we were attempting." When probed on this subject, he responded: "Some families [of brain dead patients] have been referred through clinicians on the team – others have cold called us." If these statements are true, such research depends on physicians creating such doubts and researchers preying on such desperation.

It can be argued that no harm can be caused to a brain-dead person, and such research may benefit future patients. The harm is not so much to the patient as to the family who will suffer emotional trauma in the name of hope of extending life.

One's best hope is that this project unravels before it takes off. If it doesn't, it is certain to produce inaccurate and misleading information. The published "results" will serve to fuel more such projects. This will have serious consequences to families of brain dead people, as well as to society at large.

Exploiting religious sentiments

In India, where there are deeply held religious and cultural beliefs on the revival of the dead, such a project will generate public interest and agitation with unforeseeable consequences. There are sufficient instances in Hindu mythology, as well as in the Old and New Testaments, of people being brought back to life. Such stories can take on special meaning at the time of a loved one's death.

It is perhaps to be expected that a person who aims to bring the dead back to life has an inflated sense of self-worth. Bansal is confident that he need not answer any questions about the scientific basis of his project, or disclose details of any regulatory clearances he applied for and received, the studies that preceded this research, his capacity to conduct it, the composition of his institutional ethics committee, and so on. He shrugs off the ethical significance of his research ("These are just bodies on the way to the funeral") or the consequences to relatives ("They may be traumatised for a short while but they'll get over it").

Existing regulations flawed

Bioquark has stated that it is conducting this trial in India because it will be much cheaper. Another reason is surely that it will not be permitted in the US. Indeed, it seems that all ethical and regulatory requirements have been bypassed without question in India. The trial's situation in a small town will make it even easier to avoid any future monitoring.

This project highlights a number of flaws in the regulatory apparatus for medical research. Guidelines on stem cell therapy and research, formulated by the department of biotechnology and the ICMR, state that stem cells used for other than specific approved treatment, may be used only in research. This research is subject to regulation by the DCGI. In addition, such research must be approved by the National Apex Committee for Stem Cell Research and Therapy as well as an Institutional Committee for Stem Cell Research. However, these guidelines are only guidelines, and the authorities apparently believe they cannot take any action in the absence of a law. In fact, the NAC-SCR may, within their scope of work, inquire into this trial, monitor it for unethical practices related to stem cell research and therapy being followed by the researchers, and bring them to the notice of the relevant authorities.

Bansal can also be pulled up for violating the Medical Council of India's code of medical ethics (6), for unscientific practice and research conducted without regulatory clearances, for advertising on his website (he suggests he will make dead people walk, and offers stem cell procedures for untested procedures), unscientific medical practices, and many more acts. The state medical association can suspend or cancel his registration. But there is an eerie silence from the medical councils on Bansal's malpractices.

The HMSC must give clearance for collaborative research**.** The ICMR director general who is also the chair of the HMSC screening committee is quoted as saying that this project should have come to the HMSC (1). Bansal has not applied for HMSC clearance. The HMSC doesn't seem to have inquired into the matter. Nor has this high level committee felt the need to make any kind of public statement on the ethics and science of the proposed research.

The ICMR has taken the stand that it does not have the authority on this project. The ICMR director general has also stated in a tweet that they have issued a "warning letter" to Bansal and also "refused to register" his project. The project is actually registered in both the Indian government/WHO registry (CTRI/2016/04/006893) and the US government registry clinical.trials.gov (NCT02742857), which to the public implies legal approval.

Surprisingly, the CTRI page of Bansal's trial (CTRI/2016/04/006893) shows that DCGI permission is "not applicable." But, as Bansal himself states in a television interview, the trial includes the use of drugs. Surely, the use of a drug on brain dead patients would be a new use of a drug used in a clinical trial, where DCGI permission is mandatory.

It appears that the Institutional Committee for Stem Cell Research and Therapy at Anupam Hospital is unaware of all the permissions that Bansal should have obtained from various authorities, and the various rules, regulations and guidelines that he must follow, before it granted him approval for this trial. Both the committee and the researcher are expected to be aware of Good Clinical Practices that must be followed while conducting any research.

Does the Bansal story sound familiar?

In December 1996, Dhaniram Baruah, an Indian cardiologist, conducted what was touted as a path-breaking scientific achievement -- a pig-to-human heart transplant. The recipient died a few days after the procedure. Baruah was arrested under the then Transplantation of Human Organs Act, 1994, but later released. He has not been censured or punished by government bodies or by professional associations (7).

Nineteen years later, nothing much has changed. An Indian doctor and a US biotech company have announced a study to restore the dead to life. Neither the ICMR which is to provide leadership on ethical issues, nor the DCGI which is a regulatory body, nor the professional self-regulatory associations have even issued a public statement on Bansal's announcement, let alone called for action. Surely these organisations must be held accountable for their silence, a silence which amounts to approval of Bansal and his ilk.

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Note: *E-mail correspondence and documents related to the project are available with the authors.*

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