FROM OTHER JOURNALS

Studying designs of an HPV vaccine trial

Defining the minimum standard of care in clinical trials is an ethical concern, and this informs the way researchers design a trial to test a new drug/molecule. The authors of this paper point out that given the various counts on which a study is expected to perform successfully, designing an ethically sound study has become a challenge in itself. This paper describes the possible study designs of an HPV vaccine trial enrolling HIV-infected adolescent girls in low-income settings. The designs are as follows:

- Superiority placebo-controlled crossover design: This uses random sampling for half the study population and at the end of the three-year period, unblinds the participants and offers the vaccine to the placebo group.
- Designs without untreated controls: Since the vaccine is likely to be at least somewhat efficacious in HIV-infected adolescents, it is offered to all participants.
- Designs without untreated controls, including cohorts of HIV-infected and HIV-uninfected girls: Here, the previous design is modified by studying individuals in all the study arms from a similar background with the same study endpoint.
- Open-label uncontrolled trial administering three doses of vaccine to HIV-infected girls: A cohort of HIV-infected adolescent girls is enrolled, three doses of the vaccine are administered, information is collected on its safety and immunogenicity, and the patients are followed up long enough to estimate the proportion of those developing persistent HPV infection. This proportion is then compared with published estimates from trials in older women with the same endpoint.
- Superiority design randomising HIV-infected girls to four versus three doses of vaccine: In this design, randomly selected HIV-infected girls are given either three or four doses of the vaccine to determine if the rate of infection in the four-dose regimen is lower.
- Non-inferiority design randomising HIV-infected girls to two versus three doses of vaccine: A randomly selected sample of HIV-infected girls is given either two or three doses of the vaccine, on the basis of observational data from trials showing that the efficacy of one or two doses was similar to that of the full three-dose series.

After considering the merits and limitations of each of these study designs, the authors suggest that for the purpose of assessing the efficacy of an HPV vaccine in a low-income setting, the sixth design performs the best across most criteria. This design has the maximum scientific validity, has no untreated controls, has specific returns for the study population, is feasible, and provides a minimum degree of protection to all participants. However, the first design is the most potent as far as maximum scientific validity is concerned, though it fails to provide the minimum care to all participants. The authors end by stressing on the moral need to design trials that aim to achieve the best balance between scientific validity, social values, feasibility, and protection of participants.

Lindsey JC, Shah SK, Siberry GK, Jean-Philippe P, Levin MJ. Ethical trade-offs in trial design: case study of an HPV vaccine trial in HIV-infected adolescent girls in lower income settings. *Dev World Bioeth*. 2013;13(2):95-104.

Mapping the non-medical causes of maternal deaths

When it comes to maternal deaths, the focus remains primarily on the medical causes and lapses. This study was designed to understand the social/non-medical causes in two districts of Jharkhand. The "Delay Framework" (Thaddeus and Maine) was used to map the social causes of the deaths. An average of two deaths per month was recorded in the area during the one-year period of the study. It emerged that none of the women had received antenatal care, while only 10 had received the tetanus toxoid injections. A majority of them had developed mild to severe complications during the antenatal period, but most had sought no form of care. In some cases, the local traditional practitioner had held on to the case till it was too late. Referral had been made to the district hospital, which is the first referral unit (FRU) in the area. As per the National Rural Health Mission guidelines, an FRU should have blood transfusion facilities and be able to provide surgical and emergency obstetric care. However, the FRUs in the area were too ill-equipped to offer any of these and, as a consequence, routinely referred the women to the tertiary hospital, which is in the adjoining state, 70 km away. The communities knew that the tertiary hospital had the facilities, but could not directly seek admission there, without being routed through the FRU; a significant number of deaths occurred on the way from the FRU to the tertiary hospital. Also, the transport system in place – the state-sponsored ambulance – was known to demand exorbitant amounts to transfer patients, and families lost precious time while trying to arrange for the money. This also meant massive out-of-pocket expenditure, which most families in these districts could ill afford.

India has one of the highest maternal mortality rates in the world and is struggling to lower it significantly by 2015 as part of its commitment to the Millennium Development Goals. This study becomes all the more important in the light of these facts. It is an ethical imperative for the stakeholders, especially those responsible for policy-making and monitoring of the public healthcare system, to understand the causes of maternal deaths from all standpoints, and not see it just as a medical issue. It is only after these social causes have been dealt with that maternal mortality can be better addressed.

Banerjee S, John P, Singh S. Stairway to death: maternal mortality beyond numbers. *Econ Pol Wkly.* 2013 Aug 3;48(31):123-36.

Integrating "tobacco control" with the medical curriculum

Close to 70% of deaths owing to tobacco consumption occur in low- and middle-income countries. The authors of this paper argue that making tobacco cessation a normative part of all clinical practice is the only way to reduce tobacco-related deaths and counter tobacco-related morbidity in the long-run. The contact between patients and doctors is considered the point of entry for this. It is important that doctors inform their patients about the immediate and long-term health-related problems that tobacco users are likely to face and, as the authors point out, the precondition for this is that the doctors should be aware of these problems.

However, the medical curriculum in India at present does not contain detailed information on the dangers of tobacco use.

A cross-sectional survey was conducted among all undergraduate medical students and faculty members in five medical colleges to assess the levels of tobacco use, receptivity to and practice with respect to tobacco cessation, and their readiness to adopt a more comprehensive education programme. One of the findings was that around 60% of the students (from a universe of 2585) had started smoking after joining medical college, and the percentage had increased over the four years. Only 20% of the medical faculty (from a universe of 713) reported having sufficient training or experience to help patients quit the use of tobacco. Eighty-nine per cent of the students felt that doctors should mandatorily advise patients to quit using tobacco. Close to 96% of the students felt that, as future doctors, it was important for them to receive education on tobacco control, as well as training on how to counsel patients.

The study is timely, considering the exponentially growing rate of tobacco-related deaths in India. Its novelty lies in the fact that it advocates the integration of the subject of tobacco-use with the medical curriculum. Until now, it has been the Indian state that has been concerned with tobacco-related morbidities and has mandated statutory warnings and graphic labels on tobacco products. If the medical fraternity is also sensitised on this issue in depth and if doctors adopt counselling as part of their routine interaction with patients, the problem of tobacco-related morbidity/death would be more effectively addressed.

Thankappan KR, Yamini TR, Mini GK, Arthur C, Sairu P, Leelamoni K, Sani M, Unnikrishnan B, Basha SR, Nichter M, for the Project Quit Tobacco International. Assessing the readiness to integrate tobacco control in medical curriculum: experiences from five medical colleges in southern India. *Natl Med J India.* 2013;26(1):18-23.

ARV drugs: prioritising prevention over treatment

The allocation of medical resources, especially in resource-poor settings has generated much ethical debate. This debate has assumed greater urgency in the context of HIV and the antiretrovirals (ARVs), especially in low-income countries such as those in sub-Saharan Africa. Several studies have argued that what is needed to end the epidemic is the adoption of a preventive strategy rather than only a curative one. In July 2012, the US Food and Drug Administration approved the use of Truvada (an ARV) as a preventive. However, those on the other side of the divide argued that the diversion of resources towards prevention rather than using them to treat the already affected population is unfair, especially when the drug is in limited supply. Against this background, the author asks: why should treating urgent cases be ethically superior to preventing urgent cases in the future? The author argues that unless effective preventive mechanisms are put in place, treatment will always seem to require priority, simply because the size of the affected population will never shrink enough unless prevention is prioritised. However, the author refuses to take sides and instead, insists that it is important to focus on the *context* before deciding to use ARVs for prevention or cure. Here, the context would include the efficacy and resourcefulness of the existing health system and other socio-economic conditions. The need to generate more supporting evidence of the efficacy of ARVs as prophylaxis in the context of different social settings is also reiterated.

The author concludes by saying that while much research is still needed to establish the likely impact and cost-effectiveness of the strategies for reducing the transmission of HIV, responsible implementation would involve dedicating substantial resources to careful monitoring and evaluation, HIV testing and counselling, raising awareness among communities, and structural interventions to reduce vulnerability to HIV infection.

Rennie S. Ethical use of antiretroviral resources for HIV prevention in resource-poor settings. *Dev World Bioeth.* 2013;132):79-86.

Ethics of embryo donation

A decade ago, it was estimated that the number of unused frozen embryos in the USA was 47,000 and on an average, 45,000 embryos are cryopreserved in the UK every year. This article supports the proposal that embryo donors can impose specific conditions in the choice of who the recipients of their embryos should be. The authors start from the assumption

that the embryo does not have the status of a "person" and the practice of conditional donation does not have to be as complex and onerous to organise legally as the practice of formal adoption. They go on to argue that conditional donation would encourage non-anonymity and healthy contact between donors and recipients, thus making donation a vehicle for the creation of new family relationships ("relational model") rather than a one-off event in the clinic.

However, the authors oppose the view that donors should be allowed to impose blanket conditions on the choice of recipients (denying donation to certain races, ethnicities and people of specific sexual orientations), and admit that in practice, it is impossible to ensure that even people who require specific conditions always make a fair , unbiased choice.

Frith L, Blyth E. They can't have my embryo: the ethics of conditional embryo donation. *Bioethics.* 2013 Jul;27(6):317-24. doi: 10.1111/bioe.12034. Epub 2013 May 30.

Models of contract motherhood

In this article, the authors argue in favour of a professional model for contract motherhood or surrogacy as a third alternative to the commercial and altruistic models, which are the subject of much debate. In the commercial model, both parties enter into a legal agreement for personal gain and the woman receives a fixed fee in exchange for her services. The altruistic model is based on the gift relationship, which is not legally enforceable. The terms of exchange are not fixed and surrogacy is motivated by altruism. Both models appear to have their disadvantages. In the commercial model, the woman, being motivated by monetary gain, may put the foetus at risk if she is not satisfied. In the altruistic model, the woman is vulnerable to exploitation by the potential parents. The authors state that since contract motherhood satisfies the conditions required for professionalism, ie it requires certain levels of skills and training and has a strong ethical dimension, the professional model should be adopted, Adopting this model would also make it possible to pay a fixed remuneration to the mothers, whose collective interests could be safeguarded by the formation of a professional body.

Van Zyl L, Walker R. Beyond altruistic and commercial contract motherhood: the professional model. *Bioethics.* 2013 Sep;27(7):373-81. doi: 10.1111/j.1467-8519.2012.01962.x. Epub 2012 Apr 16.

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ॐ सर्वे भवन्तु सुखिनः सर्वे सन्तु निरामयाः ।
सर्वे भद्राणि पश्यन्तु मा कश्चिद् दुःखभाग्भवेत् ॥

OM. SARVE BHAVANTU SUKHINAḤ
SARVE SANTU NIRĀMAYĀḤ,
SARVE BHADRĀṆI PAŚYANTU
MĀ KAŚCID DUḤKHABHĀG BHAVET.

May all beings be happy.
May all be free from sickness.
May all see and experience what is good and beautiful in life.
May no one be unhappy.

International Symposium on Spirituality and Ethics in Medicine

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