Solving for the Indirect Human Subject in Cluster Randomised Trials

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In 2012, a group of authors published a document entitled: The Ottawa Statement on Ethical Design & Conduct of Cluster Randomized Trials[1]. In this document, they posed and addressed six quandaries that face the implementation of cluster randomized trials (CRTs). One of these dealt with the question of who constitutes a human subject in CRTs. This question, along with the other five, arise as a result of the peculiarity of CRTs. CRTs are randomized trials that occur at the social level (i.e. randomization is at the level of large groups, communities, hospitals, etc.) as opposed to the individual randomization seen in randomized control trials (RCTs). Presently, there are conflicting notions as to whom ought to be designated a human subject in CRTs. The importance of resolving this conflict is that knowing who the human subjects are will ensure that populations affiliated with these trials do not undergo any undue risks and receive the necessary protections due research subjects. In this op-ed, I aim to use one of the CRTs cited in Ruth Macklin's Hastings Center paper [2] to concur in part and dissent in part with the explanation given by the "Ottawa authors" on recognizing human subjects in CRTs.

Case Study: A study randomizes 22 clinics (along with their community health workers) in Afghanistan. This study is aimed at testing the effect of using a rapid diagnostic test (RDT) in determining malaria status by community health workers (CHWs). Prior to this study, the standard practice, which was symptoms-based diagnosis, did not yield accurate results. The RDT group will be trained in using RDT and in managing malaria. The non-RDT group will be trained in managing malaria and be given a brief introduction to RDTs. The accuracy of both arms will be measured by collecting filter paper blood spots from diagnosed patients and testing them by PCR for malaria.

According to the code of federal regulations (45 CFR 46 Subpart A 46.102), "a human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information." It goes further to explain that an intervention comprises physical procedures aimed at gathering data and manipulations of the subject or his environment for research purposes. While the first half of this explanation is straightforward, the second half is subject to interpretation and has been debated in the literature. The authors of the Ottawa Statement argue that taking the manipulations of a subject's environment literally will mean falsely giving human subject designation to a wide population of people. They support their argument using an example of the large Hadron Collider carrying out particle physics research that may alter the environment in France and Switzerland. These authors pose the question that since both countries' environments will be manipulated, do we then conclude that every resident is a subject and thus should consent to the research work being done? I disagree with this example simply because the research component does not aim to manipulate the environment of the citizens. The scientific validity of the research in this example does not rely on the public's reaction to the environmental change. For example, if there is a deliberate manipulation of people's environment for the sake of data collection, these people should be regarded as human subjects of research. In the case study above, a clear part of the intervention is given to the community health care workers in both randomised groups. Therefore, it is easy to pick out the CHWs as subjects in this research. However,

according to my explanation of environmental manipulation above, the patients receiving diagnosis ought to be regarded as subjects as well.

To defend my reasoning for including the patients as subjects, it is important to address what patients generally consent to in clinical practise. Many times, in clinical practise, patients are informed of general procedures (e.g. diagnostic tests) for knowledge sake. Informed consent is usually only required when interventions are invasive, life-threatening or heroic. In other situations, patients are informed and they either give verbal consent or refusal to treatments or testing. Patients are not usually burdened with the technicalities of these treatments or test methods. Some may say that when a patient agrees to treatments or tests in a particular clinic or hospital, the patient can be said to have given presumed consent to the methods employed by that particular clinic. Going by this notion, it would seem that a CRT studying the efficacy of one method of treatment or diagnosis over another should not require consent from the patients. However, I argue that the notion of presumed consent creates a dangerous leeway to exclude patients from receiving some necessary information regarding the course of their treatment; it allows for medical paternalism. Another argument that has been put forward is that in a CRT like that in the case study, the physician-patient relationship is still intact and so the patients cannot be regarded as subjects. To this, I argue that as long as there is randomization and that the outcome of the intervention given to physicians is measured by the patients, the physician-patient relationship does not exempt patients from human subject status. In randomized control trials (RCTs), even though the patient-subjects consent to receive experimental interventions, the physician-researcher owes them a best interest function. Is there really a difference between giving patient-subjects experimental drugs to determine if it should be used widely by other patients and testing a novel method of diagnosis or treatment on patients to determine if this method should be widely implemented? I say there is no difference.

The onset of a research component usually requires that the four ethical principles of beneficence, non-maleficence, autonomy, and justice be upheld in dealing with patients as in dealing with human research subjects. I am not advocating for the patients in a situation like the case study to receive a ten-page consent form. Surely, a lengthy consent form will contain specific information of the intervention being given to the physicians or health workers, yet these will constitute unnecessary and burdensome information for patients. However, a simpler form stating to patients who visit clinics which have been randomized in such CRTs, that the clinics and its workers are part of a research study will suffice. This will ensure that the principle of autonomy is being upheld through and through. While it might not be necessary to gather consent from patients in the control clinics, if their personal records or bodily fluids will be collected to achieve the aim of the research, then they too need to provide informed consent. A difficulty that might arise in the bid to collect informed consent might be the time needed to ensure the validity and patient understanding of consent. However, in such CRTs, the patient population affected will not be very wide because these interventions are usually target specific. For example, in the case study, the patients that will need to provide consent are those that approach these clinics with symptoms that warrant malaria testing.

The conclusion by the “Ottawa authors” is that an indirect effect of a study intervention on an individual is not sufficient to confer human subject identity. However, I maintain that these indirect effects, under research conditions, constitute deliberate environmental manipulation. Hence, any experimental intervention that affects a physician or health workers interaction with patients for the purposes of collecting data warrants that the patients are treated as subjects of research as well. The only exemption that can be given is to patients in control groups where intervention outcomes are not measured by collecting identifying information or bodily fluids from patients.

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