Observational research where it is most needed

SUJIT D RATHOD

Division of Epidemiology, 101 Haviland Hall, University of California, Berkeley, CA 94720 USA e-mail: sujit.rathod@yahoo.com

Study rationale and justice

The rationale for this study was the identification of prognostic factors among women with cervical dysplasia. It was conducted in a south Asian country in the 1970s. Given the unknowns with regard to cervical dysplasia and development of carcinoma at the time, and the lack of consensus about which types of dysplasia would progress and become cancerous (1) it was appropriate to observe the natural history of dysplasia.

At that time, there was a similar ongoing study, also indicating that clinical equipoise was evident; its results were yet to be published. This study involved another combination of funders, researchers and research ethics boards. Aside from equipoise, additional ethical criteria must be considered, namely: justice, beneficence and respect for persons.

Justice

The importance of this sort of basic scientific investigation cannot be overstated. In the absence of evidence from randomised control trials, guidelines around cancer screening rely on data generated from observational studies. By determining the incidence and prevalence of women with carcinoma in situ, and identifying the features of dysplasia associated with progression to carcinoma in situ, this research could support health policy makers' efforts to increase capacity and to precisely target the treatment of cervical cancer. The primary beneficiaries of the findings of this kind of research would be those populations most affected by cervical cancer - who happen to be women in developing countries. The burden of research participation should be borne by a sample drawn from populations expected to benefit from the results of the research findings. Thus it is just and appropriate that women in developing countries were enrolled in this study.

At the time of this study, the regulatory framework for medical research ethics was still developing. The Nuremberg Code (1949) and the World Medical Association's Declaration of Helsinki (1964 and 1975) were both in existence , while the publication of the Belmont Report (1979) was imminent. The latter document - with its ethical criteria of justice, beneficence, and respect for persons - has particular relevance to this case study, as it was created in response to an observational research study. Yet, all three cover circumstances applicable to either or both intervention and observational research. Of the current major research ethics regimes, only the Council for International Organisations of Medical Sciences has created a separate guideline specifically for epidemiologic research -- most recently revised in 2008 (2) -- although the necessity for this approach is questionable(3). It is possible, then, to consider the conduct of this cervical cancer research study through both the guidelines in place at that time, and those that have been developed since.

Standard of care and beneficence

The most ethically contentious aspect of this study was the absence of treatment provision by the researchers for women found to have cervical carcinoma.

To require that treatment be readily available for conditions that are diagnosed as part of non-therapeutic health research creates a standard that effectively precludes much observational research in the settings where it is most needed. Additional complications would immediately arise: Must the researchers increase the treatment capacity at the regional cancer centre? Or must they start offering cancer treatment at the local hospitals? Would participants be put ahead of non-participants on the waiting list, and/or have their treatment paid for? In fact, it is not the responsibility of the public health researchers to rectify the shortcomings of the public health system; that is the appropriate jurisdiction of elected officials and civil society. It is, however, the researchers' responsibility to describe the distribution, determinants and consequences of ill health, and to identify potential means of intervention.

Thus, the limited treatment capacity in the study area is not ethically problematic. Frequently, it is the case that health research is conducted in areas of limited resources, where the *de facto* standard of care is below the standards in high-income settings. Though it may appear that the investigators were exploiting the participants' lack of access to treatment -- an ethically unsound strategy made infamous by the Tuskegee study of untreated syphilis -- they were not exacerbating the situation for purposes that would not benefit participants. It must be re-emphasised that the researchers were attempting to address a critical gap in the knowledge base around the development of cervical cancer. The knowledge gained could enable more efficient allocation of cervical treatment in these areas of limited resources.

Some may question whether this study satisfied the ethical requirement for beneficence, as many women referred for treatment of carcinoma experienced deteriorating prognoses during their lengthy wait before the initiation of treatment. By virtue of the study design, the delays that participating women experienced between the development of carcinoma, the diagnosis of carcinoma, and their entry on the cancer centre waiting list would certainly have been far shorter than for women who were not participating in this study. In spite of

the long wait at the regional cancer center, the post-diagnosis prognosis was undoubtedly enhanced for the 71 participating women diagnosed with malignancies in the study -- a clear benefit of participation.

Informed consent and respect for persons

It is not clear what information was provided to the women as part of their recruitment and enrolment process. That "women were not aware that treatment was available", on the face of it, appears incriminating. But in the light of the local standard of care, it is irrelevant that women in other countries would be immediately treated upon detection of cervical dysplasia. The relevant standard is the established, local one: women with carcinoma in situ are candidates for treatment, and these participating women found to have carcinoma were in fact referred to the regional cancer centre. In the 1970s, as now, the Declaration of Helsinki makes clear a medical researcher's primary interest is the well-being of the individual participant(4, 5); this ethical standard is satisfied by researchers providing immediate referral to the cancer centre upon detection of carcinoma, as a non-research clinician in this setting would have done.

One aspect of this case study requiring additional detail is what women were told with regard to the research question. Informed consent, by definition, must be informative; women need the necessary information to make the decision of whether or not to participate in the research study. These women would have to be told that: a) they were being asked to be participants in a research study; b) the research question concerned identification of cervical features that might predict development of cervical cancer; and c) participants found to have developed cervical cancer would be referred to the regional cancer centre. Some women might have decided that they prefer not to have their cervical health tracked, or that if diagnosed, they would not or could not avail themselves of the treatment offered at the cancer centre. Respecting individual autonomy entails provision of the kind of information necessary for a recruited individual to make an informed decision about participation. Insufficient information is available here to assess whether this ethical imperative was satisfied.

Equipoise and stopping rules

Clinical equipoise is again a concern after the publication of a longitudinal study which had been investigating a similar research question as in the south Asian country. Now, the research 'gap' concerning cervical dysplasia and development of cervical cancer is occupied by a single observational study. In this situation, investigators of contemporaneous studies concerning the same research question are faced with a dilemma: whether they would have had justification to start their own study had they known those results. In other words, once the longitudinal study had been published, was there still a state of uncertainty around the study question within the clinical community? If a reasonable clinician could believe some uncertainty remained, then continuation of the ongoing study would be justified.

Although investigators and sponsors are generally careful to conduct high-quality research, it is infrequently the case that the result of a single study is sufficient to conclusively answer a research question: replication is at the heart of science. Not only for observational research, but even with randomised controlled trials, consideration of results from several studies is necessary to resolve clinical equipoise. Statistically significant results from early studies of a research question are frequently incorrect(6), and even when correct, the strength of the early findings is often attenuated as the studies are replicated (7). Therefore, in medical research, the conclusions from a systematic review or a meta-analysis, drawing from multiple high-quality studies, are considered the most compelling.

Stopping rules feature most prominently in randomised controlled trials, when there is typically a single exposure that is being assessed for a primary outcome. Studies can be halted if an external assessment group judges that at least one pre-specified criterion has been reached. This could be so if interim analysis produced a statistically significant result which is unlikely to be overturned with additional data collection. Another criterion might be that low enrollment or retention figures indicate a high likelihood that the study will not fulfill its objectives. A third is that there is evidence of adverse events associated with participation (8). A recent example in HIV prevention (9) demonstrates that even when one intervention study is halted early, other similar studies may continue, so that the effect of the intervention can be demonstrated consistently and conclusively. In observational research, where multiple exposures and outcomes are typically being assessed, and the exposures are not being allocated by the investigator, these considerations are frequently moot.

In conclusion, it is crucial that health researchers continue to focus on the health needs of medically underserved populations. Here, the investigators were conducting observational research in response to a local reality shared by nearly all women in developing countries at that time: that there was an unknown prognosis for women with cervical dysplasia. By virtue of the marginalised status of such populations, they are also typically at greater risk of exploitation. In this case study, the research was conducted primarily with regard to the needs of the local population, and, most importantly, benefited those women who consented to participate. Researchers and their respective research ethics committees are obliged to consider clinical equipoise before and during the trial, though observational research studies are unlikely to involve early stopping rules. When multiple studies have considered a similar research question, those responsible for crafting health care guidelines can draw from the strengthened knowledge base; changing policy requires a resolution of clinical equipoise, and multiple studies are generally required to provide that resolution.

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Some ethical issues here: demands of informed consent and ethical justification for research

PRAVESH JUNG G

Department of Humanities and Social Sciences, IIT-Bombay, Powai, Mumbai, 400 076 INDIA e-mail: pgjung@iitb.ac.in

In this comment, I intend to highlight some of the bases of the ethical concerns behind the study in question (1). I argue that these concerns should be viewed not merely with alarm but also with a sense of urgency for a demand for some ethical imperativeness. The study, I argue, either misreads or downplays the role and significance of certain principles which I posit are fundamental to the framework of medical ethics (the justification for considering these principles fundamental demands a separate essay)

The concerns that I raise here are based on two characteristics of the study in question:

First, though such studies are labelled 'observational studies' as opposed to controlled experiments, they are not mere armchair introspective observations of one's thoughts. They are carried out in a social space, where the object being observed is an 'other', rather than the 'self' that is doing the observation. (The researcher-subject dichotomy can be seen as an instance of the self-other dichotomy.)

Second, the legitimacy of such a study is derived from the 'end' or the projected result that the study aims to attain. That is to say that the study is not self-justificatory.

These two characteristics respectively form the basis for two pivotal demands of medical ethics -- informed consent and ethical justification for research. These twin demands constitute the major challenges pertaining to the ethicality of a research. The paper will briefly deal with these twin demands in light of the study in question.

The demand of informed consent

It is often overlooked that though the term 'informed consent' grammatically operates as a single unit, it is constituted by two terms that signify two distinct, though interrelated, demands. The first constituent, 'informed', sets forth the demand to recognise the possibility of asymmetry of information between the researcher and the participants of the study. The second constituent, 'consent', sets forth the demand to recognise the principle of autonomy.

To accept the possibility of asymmetry of information is to acknowledge the fact that individuals may differ in terms of the scope and extent of information that they possess about the world. The principle of autonomy acknowledges, on the other hand, the view that individuals are ends in themselves, and therefore, have the right to self-determination. To recognise this demand made by the principle of autonomy is to recognise that individuals have the right to choose.

However, the principle of autonomy only assures us that all individuals have the right to choose; it does not ascertain that their autonomy also enables them to understand their choices when they actually confront them. In itself, the principle ascertains the attribution of autonomy to an agent at the formal level alone. Therefore, the demand of informed consent brings into operation the related demand for recognising the possible fact of asymmetry of information. The recognition of this possible fact poses a duty for the researcher to provide the necessary information to enable agents to understand the options that they are to choose from. Thus, it is required that the principle of autonomy be supplemented by acknowledgement of the possibility of asymmetry of information. Without this, the autonomy of an agent may merely remain a formal notion without being translated into an actuality.

Thus the term 'informed consent' posits two distinct though related demands upon the researcher: the duty to recognise the autonomous status of an individual, and the duty to provide the information that would enable agents to understand their choices and consciously exercise their autonomy.

This also provides agents (in this case potential study subjects) the following rights: the right to be treated as autonomous