Rakhal Gaitonde, Public Health Researcher, Chennai, during the development of this comment.

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Lost opportunities

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Do we need different ethical standards for observational research as compared to experimental study designs like randomised controlled trials (RCT)? Should we allow different standards of care if the research is funded and carried out by local research councils in developing countries without external sponsors? How could we carry out clinical research in resource-constrained, publicly-funded healthcare facilities without compromising the quality of care given to research participants? These questions are discussed against the backdrop of an observational research study undertaken by the national medical research council in a south Asian country in the 1970s to determine which lesions of cervical dysplasia gradually progress to malignant changes (1).

Observational research versus experimental research designs

This particular observational study, to understand the progression of cervical dysplasia to malignancy, was expected to guide a national cervical cancer control programme in resource-constrained settings in a south Asian country in the 1970s. In the absence of conclusive scientific evidence that could adequately predict the progression of cervical lesions to cancer, such research was justified, rather commended, for it promised the rational use of available resources to detect and treat cancers in a timely fashion. Nonetheless, we can discuss a number of ethical issues in this study, ranging from informed consent and the standard of care to researchers' responsibility towards research participants at the end of a study and the role of external study monitors. It must be noted that most of these issues have been debated extensively in the context of experimental study designs, particularly RCTs, and standards established (2). Can we apply the same standards to an observational study? I argue that irrespective of the nature of the study design, one must aim for the highest ethical standards for any research that involves human subjects and I elaborate my reasons below.

When an individual agrees to participate in research, s/he should have been informed about the risks involved, and there should be evidence that s/he has understood them. Depending on the subject of study, and the study design, the risks could vary in severity, as can the potential harms and benefits. One can argue that in case of an RCT, participants are at risk of receiving a less effective drug, or experiencing the previously unknown adverse effects of a new drug. It is often argued that observational studies by their very nature pose less risk and harm to participants as compared to experimental studies. In the study under discussion, however, more than 1,000 women were diagnosed with cervical dysplasia or premalignant lesion of cervical cancer. Though these women were entitled to standard treatment and care for their cervical lesions diagnosed during this observational research, they received only a referral to a regional cancer hospital with a long waiting period to begin their treatment. Thus they did not get any benefits out of their study participation except the early diagnosis of cervical lesions and in fact had to face the emotional and physical suffering associated with diagnosis of cancer. This is particularly important because these women were not informed that their lesions could be cancerous before obtaining their informed consent. This was similar to the other infamous "Tuskegee study", which is acknowledged to be unethical observational research.

Research is carried out to advance scientific knowledge in the hope that it will benefit humankind. There are numerous reasons and motivations for individuals to participate in research (3). One reason is altruism -- to contribute to the production of knowledge. Are we willing to distinguish between knowledge produced through experimental studies and that through observational research? If not, why should individuals – who may have enrolled due to the desire to benefit humankind -- be treated differently and protected by different ethical standards and guidelines based on the type of study in which they have participated?

There are common elements in the design and implementation of various research studies, particularly around the involvement of human subjects. Few researchers have made attempts to improve reporting of observational research to give it the same scientific rigour as in experimental studies. The initiative Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) has developed a checklist of 22

items to improve the quality and reporting of observational studies (4). Eighteen out of these 22 points are common to experimental study designs such as case control, cohort and cross-sectional studies. Though STROBE is intended to improve the quality of reporting in observational studies, it paves the way for a similar exercise with ethical guidelines across various study designs.

Below, I discuss some aspects of the cervical cancer study, drawing upon ethical standards and guidelines recommended for experimental studies.

Informed consent

Any research enterprise is a collaborative activity involving various stakeholders such as researchers, health professionals, study participants, communities or institutes where the study takes place, and sponsors. Each stakeholder has different interests, and different motivations to be part of the study. This can lead to conflicts of interest and even adversely affect the partnership (5). The researchers in this case were healthcare providers (doctors, nurses and other staff including laboratory personnel) in eight public hospitals providing general and specialised gynaecological care. Being staff of the public health system, they were guided and bound by the instructions and protocols issued by the ministry of health and national medical research council. The study participants were women in the reproductive age group, most of whom were illiterate and belonged to the urban communities around these hospitals. We do not have any other socio-demographic information about these women, but it is possible that they had limited access to the healthcare system. They may have believed that enrolment in the research study would give them access to, and medical attention from, qualified doctors in public health facilities. Thus, we are analysing the interactions between researchers and study participants in the macrocosm of the health system (6), including the larger socio-political context.

While obtaining informed consent from the participating women, the researchers would have used simple, nonmedical language to explain the nature of the study and the role of study participants. This is important given the fact that most women were illiterate and even otherwise, general literacy may not always facilitate medical literacy. But the researchers did not inform the participants that their lesions could be of cancer, nor did they inform them of the available treatment and care options. This can be interpreted as intentional withholding of information essential for the women to make an informed decision regarding their participation in the study. In most south Asian countries, there is a clear hierarchical power relationship between healthcare providers and patients/ healthy volunteers (as it is in this study) (7). It is often believed that the doctor knows what is best for the patient, and this trust can compel persons to participate in research if the doctor advises it, particularly if the same physician is involved in regular care as well as research activities (8).

To ensure that research participants consent only after being adequately informed, it is essential that comprehensive medical information is provided in culturally and linguistically appropriate terms. This requires collaborative efforts between researchers and community members. In this case, before enrolling in the study, the women should have been informed that their cervical lesions could progress to cancer and of the various treatment options available. They should also have been informed that they could choose not to be part of the study, and there would be no adverse consequences of their refusal. These steps in obtaining informed consent protect women from coercion to participate in research and respect their free choice (9).

Standard of care

The other contentious issue in this situation concerns the 'standard of care' that the researchers and sponsors are expected to provide to study participants during and at the end of the study. This gets further complicated when an external sponsor conducts a clinical trial in a developing country, where people have limited access to any form of therapy let alone the global standard of care (10). In case of an RCT, it is expected that the benefits of a study will be made available to participants and the entire community; in case resources are limited, they will be made available for a reasonable time according to CIOMS, Guideline 10 (2).

The case study we are discussing here is an observational study and not a clinical trial but the issue of the standard of care is still important. The absence of an external sponsor does not change the obligation of local researchers towards study participants (11). The debate on the 'global single standard of care' and the need for 'double standards' is ongoing; there are no universally accepted solutions (10,12, 13). How do we define the 'standard of care' through the public healthcare system in a south Asian country? Let us examine what could be considered the 'standard of care' in this particular case study.

We do not know the exact details of this country's health expenditure and budget, but the fact that the study was commissioned by the national medical research council in order to design a cost effective cancer control programme suggests that resources were limited. As per national guidelines, this country did not aggressively treat lesions of cervical dysplasia, though this was a common practice in other, resource-rich, western countries. The city in which the study took place had at least eight large publicly-funded hospitals providing general and specialised gynaecological care. However, these hospitals were overburdened and did not have adequate facilities for managing cancer cases. The city also had a regional cancer facility but it had an average waiting period of six months before a patient could see an oncologist and begin treatment. It seems that the local standard of care for women with cervical dysplasia in this particular country was referral to the regional cancer institute following diagnosis, and a six month wait before they could start treatment. Thus, whether or not a woman was a study participant, there was no proactive management of cervical dysplasia in this health system, and the regional cancer hospital was clearly overworked and unable to manage patients in a timely fashion. Further, this study was

designed, funded, approved and conducted by the various agencies and institutes within the national ministry of health. No external agency was involved in this study. The researchers could argue that they provided the participants with the best available local treatment options. In fact, the women benefited from their participation in the study as screening ensured early diagnosis of cervical carcinoma in situ, and those with this diagnosis got immediate referral to the regional cancer hospital. If they were not part of the study, they would have reached the regional cancer hospital at a later stage of their cervical cancers, possibly when the cancer had spread to other parts of the body.

This referral also marked the end of the researcher's responsibility towards the study participants. Once referred to the regional cancer institute, the women were left on their own to negotiate access to further treatment and care.

Here we have two groups of women with different healthcare needs, those in various stages of cervical dysplasia, and those with cervical carcinoma in situ who were referred to the regional cancer hospital.

Midway through the study, evidence became available that *all* stages of cervical dysplasia are essentially premalignant and warranted treatment to prevent progression to cancer. By this time, the investigators had identified more than 1,000 women with varying degrees of cervical dysplasia. These women should have been treated according to the new therapeutic gold standard: aggressive treatment of cervical dysplasia in order to prevent cervical cancer.

Is it possible for a south Asian country with limited resources to provide treatment which is more feasible in the developed world? Even if we talk only about 1,000 women from the study with lesions of cervical dysplasia who should have been aggressively treated as per the new evidence; neither the recruiting hospitals nor the regional cancer hospital was capable of responding to the treatment needs of 1,000 women in a timely fashion. The national medical research council should have anticipated this situation, given the fact that it was carrying out a large, long-term observational study, and was expected to provide study participants with treatment, not just early diagnosis. The medical research council could have negotiated better functioning referral links between recruiting hospitals and the regional cancer facility to create fast-track access to cancer management for the study participants. A functional referral link would also have meant that the researchers continued to follow women referred to the regional cancer facility. It can be argued that the national medical research council should have ensured that all the recruiting hospitals were capable of managing lesions of cervical dysplasia as per the available standards, that is to treat these lesions aggressively. This gained even more importance when the evidence became available to support this strategy.

Role of the external study monitor and terminating the study

Researchers are also responsible for keeping themselves updated on evidence that becomes available during the course of their study. Half-way through this observational study, a North American journal published clear evidence that cervical dysplasia is premalignant and should be treated aggressively to prevent cancers. This was a point at which the researchers should have reassessed the objective of their study. If the new evidence was convincing, it should have been used to ask the medical research council to discontinue the study. Moreover, continuing the study in spite of available evidence against it meant causing more harm to the study participants. This is where an external monitor of the study plays an important role (14). Having no direct stake or involvement in the research, an external monitor is in a neutral position to recommend discontinuation of the study in the light of conclusive evidence generated from the same study or through other publications.

Stopping the study at the right time is essential but not enough. The researchers also needed to develop a system to manage about 1,000 patients needing aggressive treatment as per available evidence. This could have been achieved through collaboration between the recruiting hospitals and the regional cancer facility. A "triage" of study participants distributing patients between the recruiting hospital and the regional cancer institute based on urgency, other risk factors, and underlying complications could have been a step towards effective and timely management of the large number of patients who needed to be treated as an entitlement of their study participation.

Conducting ethical clinical research in resource-constrained public hospitals

Most publicly funded hospitals in developing countries have limited financial, material and technical resources, and the eight public hospitals which were recruiting women in this cervical cancer study were no exception. There are three questions that need to be considered while involving such resource-constrained public hospitals in clinical research. First, what are the ethical challenges faced while conducting research in such settings? Second, what are the consequences faced by the hospitals due to their participation in research in terms of care provision to the research participants. Finally, is there a potential to strengthen health systems through participation in research?

All eight hospitals recruiting women for this study were in urban settings and provided general and specialised gynaecological care. They were clearly overworked and understaffed, and did not provide cancer care and treatment. Recruiting patients through public hospitals ensured that women who were likely to benefit through the study participation got represented in the study. Women were required to visit the centre every three months for a Pap smear. Since this was a gynaecological hospital, Pap smears were routinely conducted, and one could be confident that the hospital staff was trained to properly collect and accurately interpret the smears without harming the patients.

However, it seems that the researchers underestimated the hospitals' ability to meet their obligation to provide aggressive treatment to large numbers of women with cervical dysplasia

if research found this to be the best way to manage such cases. There does not seem to have been adequate discussion of how the hospitals were going to manage study participants apart from providing referrals to the regional cancer institute. One benefit of conducting research through the public health system is its strengthening as a consequence of research participation (). However, one must ensure that hospitals are equipped to provide standard care and treatment to research participants before starting such research activities.

In fact, this study created an opportunity for the eight public hospitals to build their capacity in the management of early cases of cervical dysplasia. This was particularly important when it became evident that all lesions of cervical dysplasia need to be aggressively treated. By the ninth year of the study, they had about 1,000 women with various stages of cervical dysplasia who should have been aggressively treated. The regional cancer institute alone would not have been able to handle this sudden increase in patient load without assistance from the recruiting hospitals. Women with locally spread cancers and other complications could have been given priority treatment at the regional cancer institute whereas other uncomplicated and early cervical lesions could have been successfully managed at the recruiting hospitals with support and mentoring from cancer specialists. These skill-building activities should have taken place before starting the study. Once the staff of these hospitals had enough experience in managing the research participants with cervical dysplasia, these services could have been provided to other women through these hospitals. This would have achieved institutional capacity building, with eight hospitals becoming able to diagnose early cases of cervical dysplasia and manage them appropriately with monitoring and technical support from the regional cancer hospital.

The aim of the national medical research council was to develop a national cancer control programme through this research. If it had built the infrastructure and expertise of these eight hospitals during and after the research, the medical research council could have actually paved the way for future implementation of a national cancer control programme. In summary, we can conclude that the public hospitals should be involved in research provided they are equipped with the resources and skills to implement ethical and scientific research, and to provide standard care and treatment for research participants. Research activities can build the institutional capacity, infrastructure, expertise and staff skills to provide better health services in the future, thus strengthening health systems.

What can we learn from this observational study conducted in the 1970s?

Researchers and recruiting hospitals should be equipped to provide care and treatment to the study participants, and not just stop at the diagnosis of disease as an endpoint of the research. Systematic plans to provide care to participants during and after the study, within reasonable limits, need to be drawn up even before recruiting participants. Researchers are obliged to make their best efforts to provide the 'highest attainable' care to research participants, irrespective of whether the study sponsor is external or local. It is advisable to assess the study periodically and check if the study objectives are still relevant. An external and neutral study monitor could play a crucial role in monitoring the study's implementation and recommend continuation or discontinuation of the research based on the available evidence. Observational research can draw upon the same ethical principles and standards that have been developed for experimental studies, though specific details may be needed to incorporate specific challenges posed by the observational nature of the study. As in the STROBE checklist, a structured analysis could be carried out to guide the ethical conduct of observational studies, drawing upon existing guidelines for experimental research like the CIOMS guidelines or the Declaration of Helsinki. Resource-constrained publicly funded hospitals should be involved in research activities provided they are equipped with the necessary resources and skills to implement scientifically and ethically sound research. Research participation could, in fact, strengthen the public health system by improving the quality of its services. Involving communities in designing, planning and implementing research can empower these communities and protect participants against exploitation.

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