3 Should continuing services have been offered to participants after completion of the study? If so, what services should have been offered?

4 Does diagnosing a condition or disease during research result in a duty (obligation) to provide care and follow-up for that condition? Is this duty the same whether the condition is diagnosed to include patients in the study or to exclude them?

5 Do the researchers have any responsibility to "take stock" of the situation at least mid-way through such longitudinal studies? Should the sponsors ask for such an evaluation?

6 Should this study have had some stopping rules, or a monitor?

7 Should this study be accepted for publication? If not, how should the results of this study be made generally known to others?

Notes:

(1) A routine screening test used for the detection of early cervical abnormalities, namely precancerous dysplastic changes of the uterine cervix, together with viral, bacterial, and fungal infections of the cervix and vagina. Cervical screening is a relatively simple, low-cost, and non-invasive method. Regular screening for cervical cancer reduces both the mortality from and incidence of cervical carcinoma.

(2) Abnormal development or growth of tissues, organs, or cells. It is the earliest form of precancerous lesion. Dysplasia can be diagnosed as either high or low grade, with high grade dysplasia indicative of a more advanced progression towards malignant transformation.

(3) A general term for the abnormal growth of squamous cells on the surface of the cervix. The changes in the cells are described as low grade (LSIL) or high grade (HSIL), depending on how much of the cervix is affected and how abnormal the cells are. HSIL is regarded as a significant precancerous lesion, whereas low-grade SIL (LSIL) is more benign, since most of these lesions regress.

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CASE STUDY RESPONSES

Knowledge vs ethics in clinical research in resource-poor settings: a clinician's perspective

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This case study of the 1970s (1) no doubt raises several ethical questions. I will however try to look at the case study from the perspective of a gynaecologist and primary care physician attempting to establish a community-based cervical cancer screening and care programme in rural Tamil Nadu.

There is enough knowledge today that cervical cancer is caused by the Human Papilloma Virus and progresses through stages of cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS) to invasive cervical cancer. This knowledge determines the modalities of screening and treatment recommended today for cervical cancer and its precursors. However, while attempting to analyse the case study to draw lessons for current practice, one needs to start from the scientific evidence that was available regarding cervical cancer precursors at the time of the study, to consider whether a study to understand the natural history of cervical cancer was necessary, and whether the study was justified in its design of following up women with proven dysplasia without any intervention, given the evidence available at that time.

Since I have no personal knowledge of the clinical scenario in the period of the study, I looked through literature on the history of cervical cancer treatment and also spoke to two senior gynaecologists who were working in premier medical institutions in India at that time. I understand that the progressive nature of cervical dysplasias (as they were called then) to cervical carcinoma was well known by the early 1970s. In 1968, Richart (2) indicated that all dysplasias have the potential for progression. However, there seems to have been a lack of clarity on how exactly each grade of dysplasia behaved and what proportion actually progressed to invasive cancer. This was an important issue, especially while evolving guidelines for treatment in high disease-prevalent resource-poor settings like India. Based on existing understanding, while carcinoma in situ was most often treated with hysterectomy, severe forms of dysplasia were often treated with an excisional cone biopsy of the cervix. Treatment for mild and moderate dysplasia did not seem to have any standard protocol and varied between individual facilities. Answers to questions

regarding the natural history of dysplasia would therefore, at that point, definitely have helped in evolving context-specific guidelines for clinical decision making.

Also, there seems to have been a widely held view that since cervical cancer was highly prevalent in the developing countries of south Asia, and there was a possibility of ethnic variations in disease pathology, studies on South Asian women were needed. While these arguments may be used to justify planning a study to understand the natural history of dysplasia and cervical cancer, how does one decide if such studies are really needed? How does one decide when the evidence generated in "developed" countries is relevant to the question at hand, and when indigenous studies are in fact needed?

Moving on, even if one were to accept that the study was indeed justified, was the methodology planned appropriate and ethical? First, did the institutions carrying out the study have the necessary infrastructure to take on a study of this magnitude? The study involved following up women with possible cancer precursors with the potential of developing into a serious, life-threatening disease. Were the institutions capable of the stringent recall and follow-up required in such cases? Given that they could not handle the final disease if it developed, were they even justified in taking on the study? Given the significant false negative rates of Pap smears, well known in the 1970s, were they justified in relying on Pap smears alone to reach an end point of CIS to begin treatment when it was likely that this already meant foci of invasive carcinoma were present in the woman? This was a time when modalities like colposcopy were being used in other countries (3,4). Other technologies were thus known and available to evaluate women with cervical dysplasia, while this study relied solely on Pap smears. Was it okay to agree on CIS as the end point for follow-up when it seems to have been common knowledge then that severe dysplasia or CIN III and CIS were part of the same continuum? Should there not have been systems for interim monitoring of such a long-term study so that changes in global clinical practice, such as those influenced by the other study published in the North American journal, would have been taken into account? If the questions that the study had set out to achieve were already answered by another study, should this study not have been terminated? Shouldn't women in this study have been given the benefit of knowledge gained from that study and offered treatment?

There are also some other questions that I would pose as a clinician. How does one balance the roles of a clinical caregiver and researcher, especially when these may be in conflict? In this study, the researchers were mostly clinicians whose primary responsibility was patient care. Shouldn't the basic principles of clinical ethics of beneficence, non maleficence and patient autonomy apply in these settings too? Aren't these also ethical principles guiding research? If one accepts this, then, in view of the long-term nature of the follow-up and the implications of not intervening, the women should have been consulted at every stage in decision-making regarding their care, regardless of their initial consent to be part of the study. In this particular case, the initial consent also seems to have glossed over several important facts well known to the researchers at that time, such as the lesions' potential to progress to invasive cancer. Patient autonomy cannot be overridden even if the clinician believes in good faith that what s/he is doing is best for the patient – though even this does not seem to have been the case here. Also, the least the clinicians could have done was to expedite treatment for these women once they developed carcinoma. That they failed to do so reveals a total lack of concern for the women in the study as compared to the research outcomes.

Then, what about public health ethics? How does one strike a balance between clinician and public health researcher? What if, truly, this study had uncovered a different pattern of progression of dysplasias in south Asian women? Would it then have been justified in its design and methodology? Would the larger good of understanding cervical dysplasia in south Asian women to benefit women in the future have been justification enough for following up women with dysplasia in this study without intervention? I do not think so. Even if the study were justified in terms of the larger public good, adequate safeguards should have been built in, so that women in this study also received the benefits of existing and emerging knowledge, whether from this study or elsewhere. Interim monitoring of results, terminating the study in the face of the results of the other study, expediting treatment for women whose dysplasias progressed in severity - all of these should have been necessarily built into the study.

This case study brings up several concerns on the regulation of research studies in developing countries including India. While the situation now is vastly changed from the era of this study, it is also true that there is an explosion of clinical trials happening now in India. Questions such as what kinds of trials may be carried out in developing countries like India, and what kinds of problems they should address, gain relevance. Even if one were to accept that certain problems relevant to our country need clinical research based here, how does one safeguard the interests of trial participants? This gains significance especially given the large scale poverty, marginalisation, and lack of literacy and information in countries like ours. How does one ensure that the marginalised are not exploited and are in a position to negotiate safeguards for their benefit in a research setting?

Research priorities in developing countries need to be driven by the sometimes unique clinical needs of these countries. However, carrying out research studies in resource-poor settings can be challenging. This can very often result in compromises in ethical standards for reasons of "practicality". The role of regulation and regulatory bodies is, therefore, crucial in such settings. This is all the more critical given that, most often, research subjects in these settings are the very marginalised.

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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