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THE ICMR CODE: A CRITIQUE AND SOME RECOMMENDATIONS

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Women's groups in India have grappled with ethics in medical research since the early '80s when blatant ethical violations during clinical trials came to light. From injectable contraceptives being tested on women unaware that they were part of a trial; inadequate follow-up and downplaying side-effects in trials on Norplant and anti-fertility vaccines, to illegal trials on quinacrine by NGOs, we have contended with non-implementation of existing ethical norms. We have also attempted to redefine the very norms themselves. Ethical violations in contraceptive trials and epidemiological research by scientific bodies which set standards for the whole country, such as the Indian Council of Medical Research [ICMR] demonstrate the need for public debate and intervention.

In 1997, Draft guidelines were issued by the ICMR seeking input from health professionals and activists. The 'Consultative Document on Ethical Guidelines for Biomedical Research Involving Human Subjects' was drafted by the Central Ethics Committee on Human research (CECHR) under the chairmanship of Justice MN Venkatachaliah, who at the time was also chairman of the National Human Rights Commission (NHRC).

Regional public debates were held in Calcutta, Mumbai, Hyderabad and New Delhi. Needless to say, women's and health groups at the forefront of campaigns highlighting violations in medical ethics were not invited to most of these meetings. Saheli had submitted a detailed critique and list of recommendations. After four years, the final document, christened the **ICMR Code**, was released in September 2000.

The Code includes many areas not covered by the sketchy 1980 ICMR Policy Statement on Ethical Considerations Involved in Research on Human Subjects. e.g. human genetics research, organ transplantation, epidemiological research and Assisted Reproductive Technologies. Widening the scope of the document is an encouraging sign of the attempt to keep pace with the challenges posed by scientific and technological developments.

However, the Code fails to acknowledge changing social trends, especially in the context of gender and class inequalities in Indian society. There are detailed recommendations (pg 9-16) about "Ethical review Procedures" and the setting up of Institutional Ethical Committees. Yet, these details appear to be bureaucratic procedural matters, and do not embody the spirit of ensuring ethical bio-medical research. Ethical guidelines should go beyond technicalities and build effective

safeguards so that the unequal power relationship between researchers and subjects is neutralised and no new avenues of exploitation of research subjects are opened up. It is crucial that the basic principles be stated clearly and unambiguously. The current document falls short of these objectives.

Contentious issues remain relating to newer technologies like genetic research, organ transplantation etc. which need to be publicly debated with groups working in these areas. As a women's organisation, we shall here address the shortcomings in the Draft in areas in which we have been directly engaged:

I. INFORMED CONSENT:

Informed Consent is central to ethical biomedical research, but has not received adequate attention. The Draft undermines the cardinal principle of informed consent in the interest of "the overall purpose and importance of research." The possibility of "waiver of informed consent" (pg 17) is unacceptable, since 'emergency' is left undefined. A new section headed "Obligations of the Investigators regarding Informed Consent" (pg 18) highlights important issues such as deception, undue influence and intimidation while giving consent; evidence of informed consent; renewal of informed consent during an ongoing trial etc. However, some issues which still need consideration are:

i. Information about potential risks and benefits should be provided verbally and in writing in, and in vernacular whenever necessary.

ii. A social worker [not the doctor alone] should be involved in counselling. During written informed consent, the signature should be witnessed by a person not related with the trial.

iii. For research involving the whole community/ large group, the consent of the village elder and/or community leader should not be considered adequate. Proxy consent should not be permitted.

iv. Where a new study proposes to use samples collected for a previous study, consent given for the earlier study cannot be deemed to apply to the new study.

v. Even when the research design involves minimal risk (e.g. only collecting data from subjects' records) the Ethical Committee should make a case-by-case judgement about waiving informed consent.

vi. Researchers should not be allowed to disclose the identity of the participants to those not associated with the trial, without seeking permission from the Ethical Committee.

vii. Health insurance should be mandatory for trial participants, and should be communicated while obtaining informed consent.

Some elements have also been added to the "Essential Information for prospective research subjects" (pg 19), for instance points (vi), xii(ours) and xiii-xv.

II. ASSISTED REPRODUCTIVE TECHNOLOGIES [ARTs]:

Instead of guidelines for research, this section of the Draft read like promotional literature for such technologies. There was a lop-sided and unnecessary emphasis on equipment and descriptions of technical procedures. The finalised Code, however, has been trimmed down to a large extent, and focuses more on the contentious issues.

The Code reveals biases which could work against the interests of certain sections who are not within the narrowly defined confines of the family e.g. single parents, non-heterosexuals etc. Persons should not be denied ARTs on grounds of sexual preference or marital status. The notion of "legitimacy" of children needs to be redefined keeping in minds the custodial rights of mothers.

Ethical guidelines should not accept social stigma attached to infertility as a norm. Societies have evolved social ways for childless couples to deal with infertility, for instance, adoption, foster-parenthood, etc.

The Code reinforces conservative attitudes by recommending matching of religious and ethnic background for donor insemination. Issues like religion and educational level have no bearing on genetic inheritance and should not be considerations during donor selection.

The Code focuses only on risks to the subject and does not touch upon other ethical issues involved with ARTs which arise out of changes in family structures e.g. who gets custody of frozen embryos after a divorce? Can a woman be inseminated with her partner's sperm after his death? In case of serious/life threatening illness which needs the biological parents' or siblings e.g. bone-marrow transplant, kidney transplant etc., should the identity of a sperm or egg donor be revealed? What are the legal aspects of these situations, relating to inheritance, custody etc.? The Code makes a sweeping statement that "There are no medico-legal problems posed by IVF-ET with egg and sperm of married couple," thus foreclosing all possibilities of debating these issues. Though it is difficult to envisage changes in laws right away, dilemmas and conflicts are bound to arise and a document on ethical considerations should take into account the changing societal trends.

III. CONTRACEPTIVE RESEARCH

Lack of separate attention to this area of research in the Draft was a serious lacuna pointed out by us. The Code now carries a paragraph on contraceptives under the general heading of "Special Concerns". This paragraph does, however, highlight three crucial issues – informed consent and information about the

alternatives available, proper follow-up -- even when a subject has withdrawn from the trial – as in Norplant, and follow-up of children born due to contraceptive failure.

Yet, we feel that the issue of contraceptive research deserves more attention. The bulk of contraceptive research is targeted towards women, a section of society that already has lower nutritional levels and poor access to health facilities. Secondly, most of the emerging contraceptive technologies have multi-systemic effects, and require more careful studies in order to ensure their long term safety vis-à-vis women's health and their future progeny.

All aspects of contraceptive research must respect the diverse knowledge and needs of women, as defined by women. Further, fertility and pregnancy are not diseases, but a normal part of a woman's life and must be understood as such. Since contraceptives are used by healthy women and men in the prime of their lives, the risks-benefit evaluation is to be different from that used on drugs/procedures for treatment of diseases. We suggest the following broad guidelines (inspired by the Canadian Women's Committee on Population and Development: Bill of Rights for Contraceptive Research, Development and Use, 1993) within which contraceptive research must be conducted:

A) Contraceptive Research and Development

1. Hazardous contraceptives,
2. and contraceptives with potential for abuse should not be promoted. Instead, such methods should be promoted which:
   - Enhance women's health and well-being;
   - Are user-controlled
   - Are reversible in the case of spacing methods
   - Meet women's needs at various points in their life cycle
   - Exhibit demonstrable advantages over existing contraceptives

2. Research must assess the degree of risk to children conceived as a result of contraceptive failure.

3. More resources must be allocated to the development of safer methods of contraception, such as barrier methods, that offer protection from sexually transmitted diseases, especially HIV; and also to the development of male contraceptives.

4. As part of formal research processes, mechanisms must be introduced which facilitate equal participation of women's health activists and potential contraceptive users in decision-making and advisory bodies involved in:
   - Setting research priorities
   - Monitoring ongoing research
   - Defining the criteria for safety
   - Reviewing research findings and assessing the acceptability of a method to proceed from one research stage to another.

5. Contraceptive research must be subject to review by multidisciplinary ethics committees.
6. There should be transparency in contraceptive research, including: criteria for determining research priorities, information on research protocols, process and findings; criteria for determining safety; funding and patent information.

B) Contraceptive Testing, Evaluation, Approval and Monitoring

1. Written informed consent must be obtained from all the participants of research trials in accordance with the guidelines laid out in Point (I) above on Informed Consent.
2. Researchers, government and funding institutions are responsible for ensuring the safety of trial participants, and liable in case of damage to health/life of the trial participants or their future progeny.
3. Participants must be informed of their right to withdraw from trials at any time. Voluntary withdrawals must get due weightage during trial evaluations.
4. To determine whether a contraceptive is appropriate for a particular country, trials must take place within that country. Participants in these trials must reflect the make-up of women who will be using the contraceptives.
5. Long-term monitoring and follow-up of trial participants and children born to them during or after trials must be undertaken to determine the effects of the contraceptive technologies over time.
6. Contraceptive trials should immediately cease if the potential arises for serious risk to trial participants.
Users' responses to and assessment of the contraceptive method under review must be recognised as valid research findings and incorporated into the evaluation process.
8. Independent mechanisms must be established to monitor research trials to ensure compliance with international ethical standards.

C. Post Marketing Surveillance:

In this age of liberalisation, it is surprising that the Draft makes only a passing mention of Post Marketing Surveillance (PMS). In fact, while equating the PMS to the Phase IV clinical trial, the Code disclaims responsibility to oversee its results, by claiming that this is "outside the purview of the ethical committee".

The Code does, however, highlight one area of frequent violation of ethics. "A physician investigator ...should ensure that patients understand and remember are yet unproven." In drugs like Depo Provera, which are easily available even over-the-counter, this precaution has not been followed, thus making a farce of the PMS.

The Code includes more specific recommendations about PMS/Phase IV trials than the Draft. (See pg 32). Yet, there is an urgent need to provide stringent guidelines

Our experience with PMS of contraceptives demonstrates the problems inherent in the concept. PMS being conducted by the pharmaceutical company which stands to gain directly, defies scientific objectivity.

Some recommendations to monitor PMS:

i. Monitoring mechanisms should be an integral part of the licensing agreement.
ii. PMS should be time bound.
iii. Information should be provided on the package of the drug/device clearly stating that it is undergoing PMS.
iv. Adequate information must include all potential side-effects, however rare.
v. Treatment plan for side effects/complications must be part of the ethical clearance prior to commencement of marketing/PMS.
vi. Mechanisms to award damages in case of complications, serious side-effects, long term problems, etc. must be set into motion.
vii. License/registration should be provisional until results of PMS are available.
viii. Results of PMS should be subject to independent expert analysis.

MEDICAL RESEARCH IN THE AGE OF PRIVATISATION

In a liberalised economy, medical research is increasingly being carried out by private institutions – NGOs, pharmaceutical companies and private colleges etc. Issues of accountability and monitoring of the quality and ethical considerations of the research have not been given adequate attention in the ICMR Code. The gains of research feeding directly into huge profits, as in the case of contraceptive research or the Human Genome Project makes monitoring by 'independent' bodies all the more crucial. While not arguing for increased statism and bureaucratic control, creative and effective ways of checking the "free-for-all" are vital.

Industry-sponsored research has given rise to a gamut of issues which need to be addressed on a priority basis. Amendment of standard international ethical codes like the Helsinki Declaration are a cause for concern, especially when viewed in the light of the watering down of the provisions for mandatory informed consent in the latest ICMR Code as compared with the 1980 Guidelines. When "efficiency-based" standards, and supremacy of "local standards", which are obviously lower than international standards prevail, there is cause for serious alarm (as in HIV drug trials in Africa).

The Code has moved ahead of the Draft which devoted only a small paragraph to "Externally Sponsored Research". The Code, in its section on "International Collaboration/Assistance in Bio-Medical/Health research goes deeper into the issue, but does not provide adequate safeguards against exploitation of research subjects from a developing country. For instance, by talking about "best possible nationally available care", the Code allows for by-passing international standards, which will work against research subjects.

Some new developments have disturbing implications. For instance, according to *The Economist*, "India promises to become a world center for testing new medicines" (January 29, 2000, p. 79). Contract-Research Organisations (CROs) which undertake clinical trials and other services for pharmaceutical companies are beginning to find a location advantage in India. Quintiles, a large CRO based in North Carolina and Covance, a CRO based in New Jersey, have started conducting clinical trials in India and are expanding their operations. Nicholas Piramal has begun a new clinical trials business, and Max India has entered into a deal with the Harvard Medical School to conduct clinical trials in India and other underdeveloped countries. According to the same news report, a Covance vice-president (global safety and medical therapeutics) expected "tremendous" return on investing in India's infrastructure for conducting clinical trials.

It is claimed that a large part of the total expenditure of around $500 million that is required to discover and develop a drug is spent on clinical trials. Phase III trials use a number of human subjects. If clinical testing can be done faster and cheaper, the additional returns from an earlier launch may fetch "millions of dollars of extra revenue to the patent's owners". Clinical trials in India can be cheaper and faster. "India's billion potential guinea-pigs suffer not just from tropical diseases such as malaria and tuberculosis, but increasingly from ailments such as cancer, heart disease and AIDS, which trouble rich countries. The head of Quintile's India venture, Ferzaan Engineer says that for some diseases this can dramatically reduce the time to commercial launch of new therapies.

The shifting of research by for-profit organisations to the Third World must be viewed in the light of these norms – both national and international— of medical research. The Code merely skims over this issue (pg 20), "Academic institutions conducting research in alliance with industries/commercial companies require a strong review to probe possible conflicts of interest between scientific responsibilities of researchers and business interests (e.g. ownership or part-ownership of a company developing a new product). While the Code leaves it to institutions to set in motion "self-regulatory processes to monitor, prevent and resolve such conflicts of interests", it does recommend that prospective participants in research "should also be informed of the sponsorship of the research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research."

Muzzling the press while reporting on biomedical research, as recommended in the ICMR Code has serious implications. The Code recommends that the reporter "submit a full written, rather than oral version, of what will be reported, so that it enables the researcher to make necessary corrections if needed, prior to publication." What are the checks and balances possible in such a situation?

New ethical guidelines, in addition to keeping pace with scientific developments, must prioritise safeguarding the rights, health and well-being of research subjects. The manner in which political ideology permeates medical research makes it imperative to develop a pro-people, pro-woman definition of "overall purpose" of research.

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