Bioethics activities in India

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أنشطة الأخلاقيات البيولوجية في الهند

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الخلاصـة: يضطلع مجلس الهند للبحوث الطبية بمهمة صياغة وتنسيق البحوث الطبية البيولوجية وتعزيزهـا في الهنـد. وقد قام المجلس في عام 1980، بصياغة الدليل الإرشـادي الـوطني الأخلاقـي الأول. كمـا نظَّـم عـدداً مـن الـبرامج التدريبية المختلفة، التي تراوحت مدتها بين يوم وستة أشهر. ويعمل المجلس الآن جاهداً على إعـداد مـنهج دراسـي أساسي لتدريس الأخلاقيات البيولوجية، يمكن تطبيقه بشكل موحَّد في كليات الطب في سائر أنحاء الهنـد. وتحظـى العلاقة بين تصنيع الأدوية وبين الأخلاقيـات بأهميـة كـبيرة في الهنـد، ولاسـيَّما في وقـتٍ تـشهد الـصناعة الدوائيـة الوطنية اتساعاً كبيراً، حتى لقد تم مدّ نطاق العديد من التجارب الدوائية إلى مصادر خارجيـة في المجتمـع. وينـشط المجلس كذلك في تشجيع إنشاء لجان المراجعات الأخلاقية وتطويرها.

SUMMARY The Indian Council of Medical Research formulates, coordinates and promotes biomedical research in India. In 1980, they formulated the first national ethical guidelines. They offer a number of different training programmes, from 1 day to 6 months. The council is developing a core curriculum for teaching bioethics, which would be applied uniformly in medical schools throughout the country. Drug development and ethics is also important in India, particularly now that the local pharmaceutical industry is expanding and so many drugs trials are outsourced to the country. The council is also very active in encouraging the development of ethics review committees.

Activités de bioéthique en Inde

RÉSUMÉ Le Conseil indien de la recherche médicale formule, coordonne et favorise la recherche biomédicale en Inde. En 1980, il a formulé les premières lignes directrices nationales en matière d'éthique. Il propose un certain nombre de programmes de formation différents, d'une durée allant d'un jour à six mois. Le Conseil est en train de mettre au point un programme de base pour l'enseignement de la bioéthique, lequel pourrait s'appliquer de manière uniforme aux écoles de médecine dans tout le pays. Le lien entre la mise au point de médicaments et l'éthique est important en Inde, d'autant plus que l'industrie pharmaceutique locale est en expansion et que le pays se voit confier la réalisation de nombreux essais pharmaceutiques. En outre, le conseil encourage activement la mise en place de comités d'examen éthique.

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Introduction

Our organization, the Indian Council of Medical Research (ICMR), is important in the region and in our country, mainly because it funds research in India. Set up in 1911 by the British as the Indian Research Fund Association, it was renamed in 1949 the Indian Council of Medical Research. Its main function is to formulate, coordinate and promote biomedical research in India through intramural as well as extramural research programmes. We have 27 permanent institutions spanning the country and 6 regional medical research centres at Dibrugarh, Assam;, Port Blair, Anadaman and Nicobar; Bhuvaneshwar, Orissa; Jabalpur, Madhya Pradesh; Belgaum, Karnataka; and Jodhpur, Rajasthan. The regional research centres concentrate on research pertaining to the diseases of their particular region, where there is often a lack of proper government infrastructure for health care delivery. Consequently, the ICMR also functions as a service provider in those regions.

Our mandate is to undertake and support research, not only basic, applied or epidemiological research but also operational research in the area of public health using a variety of tools, including those of modern biology. The ICMR fosters a research culture by improving funding, mainly for developing infrastructure. It also advocates and lobbies for certain methodologies which need to be used to carry out high-quality research; creates awareness about research, from the medical student stage to the highest level; and concentrates on methods of applying the research for the benefit of the community. Sometimes the association also works to foster community support and promote an environment conducive to innovative research.

Ethical guidelines

History

During ancient times, amongst the native cultures, people were influenced by the environment and they believed that the elements of the body were part of the cosmos. This philosophy was common everywhere. There was also belief in spirits, so it was a spirito-religious concept which guided everyone. But in those days the population was much smaller and morality was engrained in everyone so there was not so much need for enforcing guidelines. Then things started changing. In India we had the traditional system, ayurveda, and later came *unani* medicine from Persia. Another traditional system was *siddha*, which is mostly confined to the southern part of the country, and also has its roots in India centuries ago. These classical traditional systems are still recognized by the government.

There were guidelines for how a physician should conduct himself and practice and, even in those early days, it was explained that the primary concern should be for the safety and the best interests of the patients. In the *Caraka samhita*, the ancient text of ayurveda, the physician was cautioned to avoid institutional entanglements that would compromise independent judgment.

Current situation

We see the same things being stipulated nowadays as ethical guidelines, but how to go about implementing ethical guidelines is the most important aspect. In 1980, 2 years before the proposed Council for International Organizations of Medical Sciences guidelines were issued, ICMR brought out ethical guidelines which dealt with ethics committees; informed consent; clinical

trials and how to conduct yourself while doing them; and how to go about research when you are using children, the mentally disadvantaged and those with diminished autonomy [*1*]. Traditional medicine was also very much a part of it as well as publication ethics.

Those guidelines still hold true, but now modern technologies and new methods in biology have been introduced. So it was necessary to revise the guidelines and formulate new ones which would actually cover these new developments. That is how we brought out the "blue book", which was released in 2000 [*2*] (the earlier one was the "pink book" [*1*]). All institutions involved in medical research involving human beings are expected to follow these guidelines. They are available on our website, http://www.icmr.nic.in/, and the corresponding legislation is expected to go through parliament during the winter session this year (2005). Every change of government has resulted in a change in the year of legislation—it was first postponed from 2002 to 2004, but it should be passed in 2005. The guidelines actually became mandated indirectly because they were incorporated in the amendments to the *Medical Council of India Act, 1956* of 11 March 2002 and the *Drugs and Cosmetics Act, 1940* through Schedule-Y, revised and amended on 20 February 2005. So any violation is still punishable.

The revised guidelines (blue book) state 12 general principles and these form the ICMR code. So for any new guidelines, e.g. for stem cell research, radiopharmaceuticals or bioterrorism, this forms a template; whatever is actually relevant can be selected from these 12 points and incorporated. Specific principles also pertain to clinical research on human genetics and organ transplantation, including fetal tissue transplantation. Some guidelines for stem cell research have also been incorporated, including some for embryonic tissue. There are also chapters on epidemiology and assisted reproductive technology in this particular edition of the guidelines.

Two guidelines, *Ethical issues surrounding genetically modified food* and *Stem cell research and therapy* are in draft stage, a joint effort between ICMR and the Department of Biotechnology, a government funding agency for biotechnology projects. When the guidelines for genetically modified food were being formulated, it was very encouraging to see that, during the first meeting, the joint secretaries of 5 ministries came to attend, showing how important this was considered by the government.

Other national guidelines have been formulated for accreditation, supervision and regulation of assisted reproductive technology clinics in India and for behavioural research on HIV/AIDS.

If you register for federal-wide assurance in joint ventures with the United States of America (USA), alongside the requirements of the American guidelines which you have to comply with, there are 2 international guidelines, one Canadian and the other Indian, which are considered equally protective to human participants.

We have a bioethics page at the ICMR website, where we have posted an institutional ethics committee survey questionnaire, which was circulated to various institutions. There is model format for submission of applications by principal investigators to the ethics committee and a format for reviewers on what points they look for in approving a proposal. There are also guidelines for preparing standard operating procedures for ethics committees

which deal with human research. It also facilitates consultation on ethical issues.

Education and training

We get e-mail queries from researchers all over the country, from the student level up to international level. We have received a number of questions asking what the Indian position is. This prompted us to determine the status of bioethics education. Some universities had actually started the process of preparing a syllabus for teaching bioethics but there was no concordance.

The ICMR was given a planning grant from the National Institutes of Health in the United States of America to develop a bioethics curriculum. This was to include a core curriculum which would be applied uniformly throughout the country and which we hoped to provide to the Medical Council of India, the statuary body for medical education in modern medicine. We also got a training grant for applying this curriculum at various levels to show how it could help in the dissemination of bioethics education. Resource persons were identified to carry out countrywide training exercises for students, faculty, researchers and ethics committee members.

This sponsored bioethics training programme has 3 main components. One is the sensitization programme, starting from undergraduate medical students to postgraduate medical and non-medical students, institution ethics committee members, researchers and faculty members, both national and international. An international workshop is planned for 6–10 February 2006. For undergraduate students, we only have a 1-day programme at the moment, but as we conduct so many programmes on ethics our experience is that it is the undergraduate, untouched, students who are the most enthusiastic learners, then the postgraduates. We have found that university teaching staff, both medical and non-medical, are very erratic in their attention, especially as they become more senior. This can be frustrating at times, unless we keep them captive.

It has been suggested that we have an informal type of programme, teaching modules through distance education. The Vice-Chancellor of the Indira Gandhi National Open University will be consulted about having the distance education model prepared. Preliminary, informal discussions have already been held.

The second component under the training grant is short-term training for the trainers. It will start from the third and fourth year of the programme for 8 weeks for the faculty and researchers. The third component is a long-term 6-month course with the trainees moving from place to place wherever the core strength exists in the chosen topic. This is because we do not have a very strong core group such as the one at the Aga Khan University, an advantage that Pakistan has.

Every 2 years we conduct the World Health Organization/ICMR training workshops. A 3-day common module has been prepared, which we have carried out in health science universities or institutions in 6 states. The aim of this module was mainly to familiarize participants, who come from both medical and non-medical backgrounds, with the essential principles and practices of ethics in biomedical research.

It should be noted that although graduates from the traditional medical schools outnumber graduates from modern medicine, the modern medicine undergraduate students have some recourse to research methodologies whereas their counterparts do not. The postgraduate students, and even some of the academic staff, do not use

proper methodology in conducting research programmes and now these schools, which come under a separate department called the Department of AYUSH (ayurveda, yoga, unani, siddha and homeopathy), are asking us to hold ethics training programmes, first for the scientists of the councils and then for the professionals in the various institutions. We even had some of the undergraduate students dropping in on one of the workshops we held for undergraduate medical students. Their enthusiasm was very encouraging.

India is huge: modern medicine alone has more than 200 institutions. It is an enormous job and ICMR is still quite small. But we are progressing. After these workshops we had an evaluation workshop and concluded that it was necessary to produce teaching materials. We agreed on 12 topics/chapters, each of which will be written by an expert. Most of this is now complete: only 1 or 2 chapters remain to be finished. There is also a case study compilation based on the Indian experience and a set of multiple-choice questions. Some of the universities are considering including medical ethics in the syllabus in the first 3 years. The sad part is that they are not going to examine the students on this particular module. We believe that there should be some sort of assessment or credit, and the multiple choice questions would help in the evaluation.

This country is so vast that 6 universities is nothing compared to the vastness of the 29 Indian States. We have to make progress in a phased manner, but we expect that the people we have trained will carry the programme forward and have received many queries about holding such a workshop for trainers.

Drug development and ethics

As in all the developing countries right now, drug development is very important in India. The country is actually way ahead in this field, with generic formulations initially but now, because of the need to be TRIPS (trade-related aspects of intellectual property rights) compliant, research and development facilities have been increased both in the public and the private sector to bring out new Indian products with proprietary names. We produce all 3 types of drugs—synthetic, genomic and plant-based. For genomic-based drugs we have regulatory committees, but there is no proper regulation for the plant-based drugs. The regulatory system is not as good as for synthetic drugs: the situation is not being monitored. Therefore, the guidelines that need to be followed are the ICMR ethical guidelines and the Indian good clinical practice guidelines [*3*], which are "Indianized" compared to the harmonized ICH (International Conference on Harmonization) good clinical practice guidelines.

The *Drugs and Cosmetics Act, 1940* has also been amended from time to time; the last few amendments included the traditional medicine formulations. A separate chapter for ayurveda, siddha and unani medicines was introduced in Section 33-C in 1982. This relates to quality control of the formulations, the appointment of a drug technical advisory board and a drug consultative committee, provision for government inspectors and analysts, etc. Mandatory compliance with good manufacturing practice and mandatory testing for heavy metals (arsenic, lead, mercury, cadmium) in export formulations are also included in the next amendment notified on 1 January 2006.

The revised Schedule-Y of the act, notified in January 2005, was very worrying for the industry. In fact, it has been compared with the American Federal Drug Administration requirements and found to be more stringent. Revised Schedule-Y concerns regulations and guidelines for request-

ing permission for the development (preclinical and/or clinical), import and manufacture of new drugs to be marketed in India. For drug trial approval, it is mandatory that the chairman of the institution ethics committee be from outside the institution, which is not the case in most of the trial sites. This poses a problem for regulatory clearances.

The industry in India is worried, not because they have to carry out this research in India, but because these stringent guidelines will have to be followed. The US Federal Drug Administration and the Office for Human Research Protections have the ethical and regulatory guidelines of different countries on their websites. Anyone doing research in India, or any of the developing countries, will find a link on these websites to the guidelines for each country that their researchers will need to follow. This applies to Indian companies as well as to multinational companies. To a great extent, this has stopped gross violations.

There is a move now to make Schedule-Y more flexible, possibly by 2006; the bill for legislation of ethical guidelines of 2000 is in the offing.

The Department of Biotechnology guidelines for recombinant products has a 3-tier system for approval: the Biosafety Committee, the Review Committee for Genetic Modification and the Genetic Engineering Approval Committee. Efforts are being made to have a single window clearance system.

There are of course biotechnology policies from the central government and the state governments, besides the government's science and technology policies, which are supposed to be conducive to conducting clinical trials in the country. For international collaborative studies, the Health Ministry Screening Committee examines proposals.

In the past, the ethics committee members would not give approval to a proposal before obtaining permission from the Drugs Controller General of India. Many times, proposals were rejected due to ignorance of the system rather than deliberate intent. Now of course the ethics committees give approval subject to the condition that the proposal gets approved by the Drug Controller General of India or the Health Ministry Screening Committee. This will cut down the time needed.

Training

We have a studentship programme at ICMR, and demand is increasing every year: it has now reached more than 1000 applications. We have to apply very stringent measures to cut down on the numbers as it is becoming difficult to handle. However, these are the people who need to be guided very well. The encouraging thing is that these student proposals are being reviewed by the ethics committee (of their institution). They have to submit an approval certificate from their ethics committee to us. With experience, and with the feedback they get from us, they can improve the format.

It is imperative to have teaching and training programmes in ethics. This is one way in which we try to help researchers. The Medical Council of India has actually given instructions to include ethics in the general syllabus. Like other countries in the region, it used to be part of forensic medicine teaching. But what was taught was not enough, except in 1 institution in the country, St. John's Medical College in Bangalore, which has more than 40 years of teaching ethics. At one time it was confined to their own college students, interns and

staff. Now, however, they are expanding this activity. Their syllabus was actually the one the Medical Council of India instructed all the medical colleges to use as the model for their programmes.

The health universities, however, started their own programmes, all different, each with their own committee going about it in their own way. Under the Fogarty-funded programme awarded to ICMR, it is expected that a uniform core curriculum will be developed.

There is also a plan to extend the undergraduate course by 6 months for training in computers, English and ethics in the first year. The teaching of research ethics for researchers and scientists should be part of continuing medical education programmes as well, and we need to create organized workshops for students, investigators and ethics committee members. Distance education should very much be a part of this. Informed consent and ethics committee review are the 2 pillars on which the rights and welfare of participants in research programmes rest. Informed consent is taken care of by the guidelines that we already have.

How the ethics committees function

To find out how the ethics committees functioned, in 2000, we circulated a questionnaire to medical colleges and ICMR institutes. We got only 32 responses, including those from ICMR institutes, where the ethics committees were not functioning well at that time despite the fact that it was ICMR that brought out the first ethical guidelines in 1980. Some people did not even know that they (the guidelines) existed. That was one of the revelations we experienced.

We discovered that there was no legal expert on most of the committees. Appointment procedures were unethical and there was lobbying for appointment as members. Decision-making was either by consensus or by majority opinion. The number of proposals reviewed varied from 2 to 60 in a meeting. The institution which had 60 at that time now has more than 100 and they are reviewed in half a day! It would be difficult to complete reading this number of proposals. This is the situation in one of the premier institutions of our country.

In most of the institutions, maintenance of the minutes of the meeting and record keeping were very poor. Of course, there was no charge or fees for review; the independence and competence of these ethics committees was, however, questionable in most cases.

We then wanted to find out whether the situation changed after the release of the guidelines and the series of workshops on bioethics for faculty members, some of whom were also members of ethics committees. This time (2003) we circulated a 20-point questionnaire to about 1200 institutions, both public and private. By that time, the World Health Organization operational guidelines had been released [*4*]. The questionnaire was drawn up based on that along with the ICMR guidelines and also previous experience. We got 223 responses. This was somewhat better than the earlier experience, but not that much when viewed in totality.

Strangely, the colleges teaching the Ayurveda system and homeopathy produced the highest response; that was something encouraging. About 179 institutions of the 223 that responded had ethics committees. We selected 40 of the 223 ethics committees which we thought might be functioning

better and plan to do a survey with the aim of developing various training programmes and capacity-building programmes after we visit these committees to see how they function. That would amount to a sort of accreditation for the first time.

Of course, this is in the future. First we have to make the ethics committees function properly and only then go for accreditation. We need to learn from the mistakes that we encounter in the process so that we are prepared to solve problems by the time the ethics committees are fully functioning.

The state of Maharashtra has the highest number of institutions, and the greatest number of ICMR studentship proposals come from there. This shows that there is sizeable research agenda there, and, of course, the pharmaceutical companies are concentrated in this area. The other area of significant development is the state of Andhra Pradesh in the south-east, although the response from there was very low. There are also many biotechnology companies in Karnataka state, in the south-west. Uttar Pradesh state, in the north of the country, is also coming up with a lot of biotechnology companies and biotechnology parks. This gave us an insight into the current situation regarding responsiveness of ethics committees to the call of research ethics.

We are still analysing the results, but it appears that the lowest number of responses came from the eastern region. That was to be expected because the north-east is a disturbed area. It is unlikely that much research is going on and therefore there are fewer awareness programmes in those areas. We did go up to Sikkim, which is in the far north, to have a workshop, but it is not possible to go there on a regular basis, the terrain is difficult and dangerous.

There are also a number of independent ethics committees in India. This started slowly in Mumbai but it is now starting to mushroom, mainly because a lot of clinical trials are being outsourced to this country and there are also institutions now offering diplomas in clinical research. On the one hand you have the multinational agencies and clinical research organizations flooding into India in great haste, and on the other hand the regulatory bodies, the funding bodies, are concerned about how to manage the situation and stem violations. Therefore, we have had a number of workshops where multiple stakeholders, including the media, are involved and we are learning from them what is needed. As a result, we now plan to have a clinical trials registry.

We need to have strategies to develop sensitization programmes, update guidelines, formulate new ones and seek international collaboration for capacity-building. We have plenty of such activities carried out under the regional initiatives by the World Health Organization in various forums and global initiatives through the National Institutes of Health, the Wellcome Trust, the Bill and Melinda Gates Foundation and the Ford Foundation.

The Forum for Ethical Review Committees in Asia and the Western Pacific

The Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) was set up in 2000, and has a meeting every year. It worked rapidly in 2 of the World Health Organization regions, the South East Asia Region and the Western Pacific Region, to educate ethics committee members. Since the Secretary General of FERCAP was also a member of ICMR, we benefited enormously through her experience in formulating the guidelines for the functioning

of the ethics committee. In fact, the chapter in the ICMR 2000 guidelines on the ethical review mechanism was a result of that [*2*]. Then followed the translation of operational guidelines for ethics committees. A number of countries, e.g. Thailand, Indonesia, the Philippines, have opened up their national chapters under the FERCAP initiative.

For the first time in 2002, we held an ICMR–FERCAP workshop for developing standard operating procedures for institutional ethics committees under the FERCAP initiative. There were 43 items in total—how to submit the proposal; how to review the proposal; how to expedite the proposal, etc. These have now been reduced to 23 after a number of other workshops, but the list is not yet finalized. Till it is, we have posted on our website the guidelines for preparing standard operating procedures. These are expected to be followed by every ethics committee before they actually start reviewing proposals.

The chapter for India was initiated in 2002 but has only recently been registered. So we will be starting the programme with these objectives: establish and foster communications between ethics committees in India; act as a national collaborating agency; organize meetings and symposia; assist in the development and implementation of standard operating procedures; facilitate training opportunities; and coordinate with other global bodies. Now we have FERCAP, Latin America, Eastern Europe, the African countries, Canada and the United States of America as regional chapters. There are also a number of nongovernmental organizations and other public sector and private sector bodies, which have joined these for a under a common "Strategic Initiative for Developing Capacity for Ethical Review" (SIDCER).

A number of colleagues from Pakistan have mentioned that they were very much in tune with the culture of the subcontinent but they could not come under the FERCAP region because of the Asia–Pacific regional distribution. They are part of the World Health Organization Eastern Mediterranean Region, but their cultures are totally different; they would actually like to be part of this initiative, the Asia Pacific Region. Perhaps we will find a way.

Conclusion

In summary, what we have done is formulate guidelines, fund workshops and constitute the Central Ethics Committee, which is a national committee of the ICMR. We also have a national ethics committee at the Department of Biotechnology but when it comes to biomedical research, it is the ICMR's Central Ethics Committee on Human Research only which sees proposals of national significance. If the institutional ethics committee comes across a problem which has a national significance, or if there is policy matter involved, then it is referred to us.

Now, because of the outsourcing of research, samples are being sent to India because of the expertise that is available here. We actually have guidelines for exchange of biological materials going out of the country, but not for what is coming into the country. This is an example of the issues which are discussed by the Central Ethics Committee.

We have also produced the curricula and carried out sensitization programmes, an ethics committee survey, the FERCAP initiative and the Forum for Ethical Review Committees in India initiative and collaborated at an international level with

countries in Europe and North America and also South East Asia, mainly through World Health Organization initiatives.

Collaboration with a number of countries and networking is the sort of global and regional initiative that is required now. We have to join forces so that our people are not exploited. There have been a number of reports of unethical practices in our country regarding stem cells. One proposal on stem cell research with an external agency was not permitted to go ahead in India on account of this because it was brought to the attention of the authorities concerned. Now we understand that it has been moved to another developing country where it is thought they found an easy outlet, taking advantage of the increasing demand for a cure generated by the helpless situation of terminally ill patients or those affected by degenerative disease.

But even in India, we need to be more vigilant. Such things are happening and the ICMR cannot police everything: the population is very large—more than 1 billion. So education in bioethics, good clinical practice and drug vigilance are important.

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