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BIENNIAL REPORT OF THE ETHICS REVIEW COMMITTEE (ERC), 2007–2008

1. At its 47th Session, held in May 2005, the Governing Council of the International Agency for Research on Cancer approved a Resolution (GC/47/R9) making fundamental changes to the arrangements for ethics review and procedures at the Agency (see document GC/47/12 Rev.1).

2. The Director was asked to report on the implementation of the new ethics review system at the following Governing Council session (see document GC/48/13).

3. In 2006, the new IARC ethics review system was created. There are two distinct components:

- **The IARC Institutional Review Board (IRB):**

  The IRB is composed of nine members from a variety of backgrounds. Five members come from outside the Agency and four from the Agency staff. The Board meets every two months in Lyon to review those IARC projects which have been submitted for ethical evaluation.

- **The IARC Ethics Review Committee (ERC):**

  The ERC is composed of nine senior members from the international community. The Committee will ensure, to the extent that is possible, that international consistency and completeness regarding ethical approval is achieved. This committee will also play a guiding role when the IRB consults it for its views and advice.

4. Professor Charles Gillis, former Chairman of the National Multicentre Research Ethics Committee for Scotland, UK, acts as IRB Convenor, provided some initial advice to IARC staff and training to IRB members on matters of ethical concern. The Scientific Coordination Office is responsible for ensuring that all relevant IARC project proposals go through the ethics process and provides the secretariat for both bodies.

5. The ERC was created in order to bring its global expertise to answer certain controversial issues within project proposals and to monitor the work of the IRB. This committee meets twice per year, one meeting being held in Lyon in conjunction with one of the bi-monthly IRB meetings in order that the two committees can consult on matters of concern. The other yearly meeting takes place in turn in one of the WHO Regions where IARC has on-going scientific activity.

6. The membership of the ERC is as follows:

- Professor Clement Adebamowo (Nigeria), surgeon and bioethicist
- Dr Kazem Behbehani (Kuwait), former Assistant Director-General at WHO/HQ
- Mr David Byrne (Ireland) (Chair), former Commissioner of the European Union
- Professor Ketayun Dinshaw (India), former Director of Tata Memorial Cancer Centre in Mumbai
- Ambassador Mireille Guigaz (France) (Chair, IRB), former Déléguée Générale of Cancéropôle Lyon-Auvergne-Rhône-Alpes
- Lord Mackay of Clashfern (United Kingdom), former Lord High Chancellor of Great Britain
- Professor Edith Olah (Hungary), oncologist and President Emeritus of EACR
- Professor Jae-Gahb Park (Republic of Korea), former President of the Korean National Cancer Center
- Dr Luis Pinillos Ashton (Peru), former Director-General of the Peruvian National Cancer Institute and Minister of Health in Peru

7. The membership of the IRB is as follows:

- Professor Jean-Pierre Boissel
- Dr Paul Brennan (Head, Genetic Epidemiology Group, IARC)
- Dr Marc Guerrier
- Ambassador Mireille Guigaz (Chair)
- Ms Ghyslaine Martel-Planche (Molecular Carcinogenesis and Biomarkers Group, IARC)
- Mr Bernard Pedeux
- Dr Martyn Plummer (Infections and Cancer Epidemiology Group, IARC)
- Dr Pierre-Jean Souquet
- Dr Bakary Sylla (Infections and Cancer Biology Group, IARC)

8. IARC must ensure that permissions and approvals granted by the countries participating in all research in which it is involved in any capacity be obtained before the research starts and give advice, including that the country withdraw from the study if difficulties cannot be overcome. The major role of IARC in ethical appraisal is thus as *the final common path* for assurance to the international community that whatever constitutes ethical approval, transparently demonstrates the fundamental principles of respect, beneficence and justice. IARC is the guarantor of protection for

study participants by its insistence on internationally consistent and complete ethical review of research. This is currently addressed by the two-level ethics process established at IARC.

9. Since January 2006, the ERC has met in Peru (11–12 January 2007), Mumbai (16–17 January 2008) and Kuwait (15–16 December 2008). Four joint meetings of the ERC and IRB have also been organized at IARC: 9–10 January 2006, 8–9 June 2006, 11–12 October 2007, 23–24 June 2008. Please see the table in Annex I for the topics discussed. The latest report of the IRB to the ERC is also attached as Annex II.

10. These meetings have provided guidance for a variety of issues including special considerations on research in low- and medium-resource countries, standards of care (Annex III) and insight into local ethics frameworks.

11. The ERC in coordination with the IRB has approved and recently updated the Standard Operating Procedures (SOP) and its overarching document i.e. the Rules and Procedures (RAP). Both documents are available on IARC's ethics website (http://ethics.iarc.fr/Documents/index.php). The questionnaire for applying to the IRB is constantly evaluated and updated where necessary. Training sessions were organized for the IRB.

Annex I: Summary of ERC and joint IRB/ERC meetings since 2006

Date	Place	Type of meeting	Topics discussed
9–10 January 2006	IARC	Joint IRB/ERC meeting	- Ethics training - Scientific evaluation of IARC projects - IARC submission procedure - Terms of reference for the ERC & IRB - Data & Safety Monitoring Committee - IARC questionnaire - Standard Operating Procedures (SOPs)
8–9 June 2006	IARC	Joint IRB/ERC meeting	- SOPs - IARC Code of Good Scientific Practice (for information only) - Questionnaire, guidance & review process documents - Ethics website - Report from IRB to ERC - Remit of each committee - Ethics Committees Training Programme - Consent of minors - Ethical assessment of research sites - Knowledge of the law - Data collected for one purpose & used for another - Confidentiality/anonymisation - Biorepositories
11–12 January 2007	National Cancer Institute, Lima, Peru	ERC meeting	- Report from IRB to ERC - IARC Code of Good Scientific Practice - Ethical issues in Peru - Repository of knowledge - Local ethics committees - Research in low and medium-resource countries - Role of the IRB - Data & Safety Monitoring Committee - Funding from industrial sources
11–12 October 2007	IARC	Joint IRB/ERC meeting	- Presentation of the Role of the Scientific Coordinator - Report from IRB to ERC - Training exercise - IARC Code of Good Scientific Practice (for information only) - Rules and Procedures (RAPs) - SOPs - Attitude of biomedical researchers in West Africa to ethical review of collaborative research - GC report on IARC funding from industrial sources (GC/49/14) - Nomination of a Scientific Overview Committee - Data & Safety Monitoring Committee

Date	Place	Type of meeting	Topics discussed
16–17 January 2008	Tata Memorial Centre, Mumbai, India	ERC meeting	- Ethical Issues in biomedical research in India and South East Asia - Bioethics: Challenges in clinical & translational research in the developing world - IRB Organization in TMC - Standards of care issues - Universality and its limits of research bioethics - Compensation for research-related injury - IARC-Studies in India: ethical issues - Ethical benchmarks for vaccine trials in India
23–24 June 2008	IARC	Joint IRB/ERC meeting	- Standards of Care - Survey on IRB review application procedure - IARC Scientific Overview Committee for one project - IARC Code of Good Scientific Practice (for information only) - Report from the IRB Chair - How is the IRB working
15–16 December 2008	Dasman Centre for Research & Treatment of Diabetes (DCRTD), Kuwait	ERC meeting	- Report from the IRB Chair - Report of the ERC to the IARC Governing Council - Update on Standards of Care - Update on SOPs and RAPs - IARC Code of Good Scientific Practice (for information only) - Ethical issues and religious beliefs in the Muslim World and Middle East - Ethical review systems in research in Kuwait

Annex II:

REPORT ON THE ACTIVITIES OF THE IARC INSTITUTIONAL REVIEW BOARD (IRB) January 2008 – December 2008

Mireille Guigaz, IRB Chair

Members

Dr Marc Guerrier, Deputy Director of the Department of Ethics Research at University Paris II, was nominated as a member of the IRB in September 2008 to replace Professor Maxime Seligmann and attended his first meeting on 29th September. The composition of the rest of the committee remains unchanged:

External members:

- Professor Jean-Pierre Boissel
- Dr Marc Guerrier
- Ambassador Mireille Guigaz (Chair)
- Mr Bernard Pedeux
- Dr Pierre-Jean Souquet

IARC staff:

- Dr Paul Brennan (Head, Genetic Epidemiology Group, IARC)
- Ms Ghyslaine Martel-Planche (Molecular Carcinogenesis and Biomarkers Group, IARC)
- Dr Martyn Plummer (Infections and Cancer Epidemiology Group, IARC)
- Dr Bakary Sylla (Infections and Cancer Biology Group, IARC)

Professor Charles Gillis continues to provide advice to the IRB and IARC staff when required.

Governance documents

The Standard Operating Procedures (SOPs) and Rules and Procedures (RAPs) had been revised in October 2007 and posted on the ethics website in provisional format until the end of 2008. The two documents had also been sent to the WHO Ethics Review Committee for their input. After incorporation of comments received from the WHO ERC plus those made by IRB members, the final versions are now submitted to the IARC ERC for approval.

IARC Scientific Coordination Office (SCO)

An ethics database has been created by SCO in order to centralize all information concerning the IARC ethics process. This database is ultimately intended to be used as a tool to extract information as well as to store information for both IARC staff and ethics committees. IRB and ERB members have access to this database via the ethics website (http://ethics.iarc.fr/) using a personalized username and password. The database contains information about all projects which have been submitted to the present IRB since February 2006 (e.g. reference number, type of study, start and end dates, funding details, etc). In its November 2008 meeting, the IRB requested that SCO submit a report concerning the follow-up process of projects as detailed in the ethics database. It is also now possible to consult the documents of past IRB and ERC meetings (presently just for 2008).

Workings of the IRB

The Board has found that holding IRB meetings on a two-monthly basis works well for both Board members and IARC staff. Since January 2008 five meetings have been held in February, April, June, September and November (June meeting took place within the joint IRB/ERC meeting). Since 2006, the Board has built up a solid experience base and members consider the meetings to be constructive, productive and hopefully they are perceived as positive by the IARC staff. Future activities to be taken into consideration would be strengthening of relations between the ERC and IRB and the organization of further formal ethics training for the IRB.

Projects

Between January 2008 and November 2008, 35 projects were evaluated by the IRB.

Over the past three years, the present IRB has evaluated 94 projects as follows:

- 90 were cleared after ethical review including those given conditional clearance
- 3 were rejected
- 1 was considered not to be within the remit of this IRB.

Annex III

Thoughts on the Care, including Standard of Care, for Participants in IARC Studies

Charles Gillis, IARC Ethics Convenor

Background

The question of care for participants in IARC studies has not been routinely considered by the IRB in their secondary ethical assessment of IARC studies. This question normally falls to the IRB of the IARC collaborator's host country – the committee of primary ethical review.

Most research at IARC is carried out by scientists rather than medical practitioners. Researchers at IARC may thus be less familiar with what is involved in finding suitable medical collaborators in the countries they collaborate with and in understanding the nuances of delivering appropriate medical treatment. Most studies at IARC involve collaboration. This collaboration usually takes place within countries with diverse medical backgrounds and often with a range of countries, some of low to moderate economic status where ethical norms may be variously displayed and to whom particular ethical consideration is owed.

Most research at IARC is epidemiological in nature and involves access to any combination of data, tissue and records. Normally any intervention for research purposes only takes place in the context of routine medical treatment. Clinical trials will be increasingly carried out.

Introduction

This paper was requested by the Chairman of the IARC Ethics Review Committee at their meeting in Mumbai on 16–17 January 2008 following further discussion at the joint IRB/ERC meeting on 23–24 June 2008 in Lyon to help clarify the responsibilities of the IRB in relation to the standard of care for research participants.

The question of standard of care arose in response to a series of presentations by the staff of the Tata Memorial Centre in Mumbai demonstrating a variety of views on this topic. The presentation of a clinical trial, the first clinical trial to be approved by the current IRB, carried out in India giving two doses of anti-HPV vaccine compared to three to determine whether the efficacy of the vaccine was sustained, focused attention on the variety of views concerning standard of care. The Chairman and members of the ERC were concerned that the IRB might be seen to be neglecting its responsibilities if the IRB was not routinely addressing the issues involved in the provision of care to participants, not only in clinical trials, but in the main non-trial epidemiological studies conducted by IARC.

Definition of Standard of Care (for participants in research studies)

Standard of care is defined by Cancer.Net as "a set of common guidelines that are followed for the diagnosis and treatment of a certain type of disease" (1). This implies that the standard decided upon will be determined before a study starts. This term often includes the care given to participants in research studies.

Views on standard of care

There is a wide range of views on the provision of care for research participants from investigators taking complete responsibility to having none. The initial view expressed by the IRB/ERC in Lyon was that IARC had to give careful consideration to the needs of participants in low- to medium-resource countries and that any medical care given should be the best the country concerned could provide. If that level of care was beyond either the resources of the participating country or the sponsors of the research, the study should not be carried out in the country concerned.

My personal view based on my experience both as a researcher and as a participant in a number of research studies is as follows:

- I would expect care for any condition found, whether directly related to the study or not, if a participant in a **clinical trial** of a new therapy or screening technique,
- I would like the organizers of **epidemiological studies** to arrange for the treatment of any condition they diagnosed in the course of the study. I am aware this is possible in countries with well established and population-based health services but problematic in low- to medium-resource countries.

The opinion of the MREC (Multi-centre research ethics committee for Scotland 2003) in relation to clinical trials is that the best treatment that can be provided locally for the condition being studied should be provided in contrast to the best possible treatment available anywhere. Thus the view of the IRB/ERC coincides with that of a committee routinely dealing with multi-centre applications for ethical review.

What should the correct view be?

'Ethical discourse is concerned with the search for justification of our actions' (2)

The current IARC questionnaire used by the IRB is based on that in use in the UK (3). It, in turn, was based on an outworking of "the four principles" underpinning many questionnaires used to determine whether a research project is ethical, namely, autonomy, beneficence, non-maleficence and justice (2).

'Reducing a rule to its principle says that for the purpose in hand, the principle is not questioned or further defined unless new rules are created' (2)

As the IARC ethics questionnaire has been built on 'the four principles', it is logical to consider if setting a standard for the care of research participants can be accommodated within these.

The "four principles"

Beneficence means the conduct of a study in a particular geographical area should confer potential benefit on a participant and their host community. This means ultimate benefit through understanding of and application of the outcome of the research, not using the research project as a personal health service.

Autonomy means respecting participants by treating them in a manner researchers would accept if they were themselves participants. This includes informing them of the risks of the study. The consent obtained implies informing participants about and possibly instigating and providing treatment for conditions found as a result of the conduct of the research.

Non-maleficence always means that the conduct of the study will do no harm. Though this cannot always be guaranteed this implies that if the study involves risk to the participants, an appropriate and safe remedy will be provided.

Justice or fairness. Belonging to community or country confers responsibilities. Participation in medical research by all sections of society including the vulnerable is one of them. If this is to be invited the consent obtained must demonstrate understanding of what the study is about, including its risks, and what remedies can be provided.

The current edition of the textbook of Law, Medicine and Ethics affirms the place of the four principles but also goes on to comment that they are by no means exclusive (1).

Professor Downie, Editor of the Oxford Dictionary of Philosophy, suggested using the Declaration of Helsinki (4) – the cornerstone of research ethics as a source of principle. The objection that this is not primarily a document derived purely from philosophy can be overridden by the fact that it is representative of the current opinion of medical associations worldwide. The Declaration of Helsinki too has its detractors. It has been recently criticised as paternalistic and for failing to address the full scope of ethically responsible research (5).

The new version of the CIOMS guidelines on epidemiological studies (2008) opens with the four principles (6). The purpose of this paper is to justify a correct ethical view of the responsibility of the IRB in considering standard of care even though most documents on the ethical principles for the conduct and ethical assessment of research do not mention standard of care directly.

Declaration of Helsinki (2004)

Standard of care is not directly referred to in paragraphs 30 and 31 of the Declaration of Helsinki (4). Indeed the care of research participants is outside the section on basic principles for medical research. However there is a clear recommendation to give the patient "access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study".

The CIOMS international ethical guidelines for biomedical research involving human subjects (2002) (7)

Standard of care again is only indirectly mentioned in the commentary on p. 82 following the guideline (21) for sponsors: 'sponsors are in general not obliged to provide health care services beyond what is necessary for the conduct of the research; although it is morally praiseworthy to do so'.

CIOMS guideline on the conduct of epidemiological studies (2008)

This is elaborated in the new CIOMS guideline (2008) on the conduct of epidemiological studies which has in addition been amalgamated with the 2002 general clinical research edition. Guideline 21 has been expanded and states that 'external sponsors are ethically obliged to ensure the availability of some health care services essential for the safe conduct of the research'. The thrust of the guideline commentary (lines 2575-2616) is that whatever medical services are provided, directly or indirectly related to the research, they should be properly laid out and agreed to in advance of the start of the study. The moral obligation to provide services is repeated but so is the statement that sponsors are not obliged to provide health care services beyond that which is necessary for the conduct of the research. However they do insist that if the research involves screening for a particular condition then treatment for that condition should be provided. Also 'when prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should advise as appropriate, or refer them for medical care'.

Further brief comment from the literature

Most of the literature on standard of care relates to clinical trials. That relating to the care of participants in population studies in public health is sparse. Most contain the inference that care should be provided. I have found no evidence to show that care should not be provided to members of a research study, though there is criticism of offering care to members of a research study lest it be construed as an inducement.

The most important ethical feature of participation in a research study involving risk is the consent obtained. Principle 15 of the Declaration of Helsinki states 'medical research involving human subjects should be carried out only by scientifically qualified persons and under the supervision of a clinically competent person. The responsibility for the human subject must always rest with a medically qualified person and never rest with the subject of the research, even though the subject has

given consent'. However Principle 5 states 'in medical research on human subjects, considerations related to the wellbeing of the human subject should take precedence over the interests of science and society'. Principles 5 and 15 could be interpreted as including the provision of care to research participants.

Macklin (2008) (8) comments that the term 'standard of care' has been applied in different multinational research contexts perhaps unwisely because of its ambiguity. She states the argument clearly. On one hand 'the ethical obligation to members of the control group is limited to whatever is the standard of care in the community or country where the research is carried out. On the other, that when a proven intervention exists anywhere in the world it should be provided to the control group even if that intervention would not be available outside the clinical trial in the developing country.'

The WHO consultation on 'not whether but how' in relation to the provision of the best treatment for Aids showed that in that context ethical opinion has moved forward. Macklin also states there is a growing consensus for providing a state-of-the-art prevention package to participants in biomedical prevention trials. She also makes the following relevant points:

1. It is a mistake to consider no care a standard of care.
2. When circumstances change so can ethical thinking about obligations to research participants.
3. Providing treatment to participants who become sick is one way among others of maximizing health-related benefits. (*Without offering an inducement to participate – my italics).*

Standard of care in IARC studies

Clinical trials

Most discussion in Mumbai focused on clinical trials. There was agreement that medical treatment must be provided for patients in cervical screening studies including vaccine studies in which IARC participates. The ERC seemed satisfied with the position in Mumbai where appropriate care, rather than the best standard of care available anywhere is provided by local clinicians. There was also tacit agreement in Lyon that care of participants and standard of care should be discussed in all subsequent IARC trials. Perhaps it is unnecessary to distinguish between the provision of care for participants and standard of care if whatever care is to be given is clearly described in advance in the protocol. This is not the decision of the IRB but of the ethics committee of primary review.

Epidemiological Studies

Many IARC studies simply abstract data, clinical observations and tissue reports from the medical records of patients in *the course of* or *after* their treatment (9). Named medical records of the patients studied are retained in the host country for follow-up purposes. There is never any patient contact by IARC and there is always complete anonymisation of patient data at IARC.

There will always be social and psychological factors relating to the presentation of findings which will be of concern in the presentation of epidemiological studies (CIOMS 2008). The ethical review by the host country is not an argument for omitting any care for research participants or standard of care issues from consideration by the IARC IRB.

Clinical and epidemiological studies

In both clinical and epidemiological studies where there is a clinical intervention, every effort should be made to ensure that the study is not a route to obtaining expensive medical treatment. This seems somewhat against Macklin (2008) (8) in her discussion on AIDS where she feels that treatment should be provided regardless. In general, studies of conditions involving complex treatments should not be carried out in countries which cannot provide these.

Variations in Higher or Best Standard of Care

Hyder and Dawson (2005) (10) consider that studies in which many patients or participants are not receiving the highest level of care available in other settings in which the research is being carried out, present great difficulties to the sponsors in defining the standard of care. Wendler et al. (2004) (11) have proposed a compromise that may allow ethics committees to accept less than the best treatment for all participants for research studies that satisfy **all** the following criteria:

- *Scientific necessity* – The literature suggests that the project be carried out best in this location due to the characteristics of the population.
- *Relevance for the host community* – The cancer affects this population greatly and studies into its prevention and/or causation might be beneficial.
- *Sufficient host/community benefit* – The conduct of the study might confer better health on some members of the community.
- *Subject and host non-maleficence* – The conduct of the study would do no harm to members of the community.

There will be many interpretations of the above criteria. Some of them overlap. This illustrates the importance of keeping to an agreement not to carry out the study if necessary complex treatments cannot be carried out at every location.

Wendler et al. (2004) (11) make an interesting point:

'Many international studies are carried out in locations where there is the assumption that appropriate treatment can be provided. In developed countries, including the US there are numerous examples of local deficiencies in medical care, particularly for groups that are poor, lack health insurance or are members of ethnic minorities'.

This means that a locally available standard of care may not be ethically permissible.

Ancillary Care (12)

Another related and entirely logical topic totally consistent with my own view has emerged in the recent literature. It is called ancillary care and is defined as 'positive obligations on behalf of researchers and sponsors to provide care that participants need but that is required neither to successfully answer the researchers' scientific question nor to avoid or mitigate harm resulting from participation in the research'. Existing ethics guidelines do not address these issues.

The authors suggest three questions for ethics committees:

1. What ancillary care needs are likely to be encountered?
2. Are the study procedures likely to reveal conditions that will need to be addressed?
3. Can they be met by the existing local health care system?

This means that a number of researchers and ethicists agree that standard of care should include ancillary care. It is not clear what happens to a research application if these needs cannot be met.

Implications for site-specific review at IARC

For the host country:
Current Standard Operating Procedures now require that the arrangements for research participants be addressed by the primary IRB, i.e. the ethics committee of the host country.

For the Principal Investigator at IARC (PI):
This means that standard and ancillary care issues should now be included together with local rules for confidentiality, recontacting patients for follow-up and decisions on who has access to the data for consideration by the PI and the primary ethics committee of the host country for all studies in which a medical intervention is included. As far as standard and ancillary care is concerned, only those with legal responsibility for the care of the patient can be collaborators in the ethical review of standard or ancillary care (4).

For the IRB:
The IRB is responsible for ethically reviewing the actions of the PI with respect to standard and ancillary care. Despite IARC being a committee of secondary review the current status of IARC will incline the ethics committees of some countries to look to it for guidance. This interchange of views would be the responsibility of the Principal Investigator. Regardless of which area of the ethics review is being considered, no IARC study could start on the sole opinion of the committee of secondary review. If no arrangements for ethical review exist in the country or community participating in the study, it is the responsibility of the Principal Investigator together with the sponsor to initiate these (13).

For the Office of the Scientific Coordinator:
The Office of the Scientific Coordinator can assist the IRB by the provision of primary ethical approvals and collaborators' CVs.

CONCLUSION

Standard of Care for participants in research studies carried out by IARC includes the general care of research participants while in research studies involving any clinical intervention. It is clear that any paper on the problem of standard of care cannot allow for the myriad of settings that might arise. It would be wrong to try. It is far better to proceed on a case-by-case basis. In the context of research studies I have seen reviewed by the IRB, the standard of care which should be given to participants in research studies need not be the best available anywhere but the best that can be equitably provided for participants in the countries or communities participating in the research. This is despite the move to best care available anywhere. A single question should be sufficient, asking if there has been a medical intervention and if so, whether care of research participants has been considered. It is worth bringing the content of this paper to the attention of members of the IRB but not worth the addition of the many questions needed to define each of the many problems that will arise. That difficult task is the responsibility of the Principal Investigator, those recognised as collaborators and the Ethics Review Committees of the host countries.

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