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OPINION INTERNATIONAL EN

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OPINION ON THE ETHICAL ISSUES OF CLINICAL RESEARCH IN DEVELOPING COUNTRIES

SUMMARY

The National AIDS Council has, on several occasions, underscored the importance of the ethical principles applicable for clinical research and voiced concern on the duty to respect trial participants. These principles are central to an almost permanent debate, which was re-fuelled at the end of the 90s by the implementation of trials or research conducted jointly in several countries with different levels of development. In an article called " The Shame of Medical Research ", David Rothman relayed in a major journal a controversy generated in 1997 by HIV trials in developing countries.

For the Council, it is not only trials, but all clinical research conducted in the South, that must be reviewed. Over the past few years, various proposals have been put forward to address the issues of research in developing countries. The Council acknowledges such progress but does want to re-emphasize certain principles that have at times been disregarded and to suggest possible ways to put them into practice.

1 IS THE ETHICAL FRAMEWORK ADAPTED TO RESEARCH IN THE SOUTH ?

Clinical research and the related ethical framework are part of a constantly evolving process fuelled by various controversies or by the transformations of the research context. The 1997 controversy started during a period of high increase in the number of trials in poor countries and contributed to the revision of guidelines sometimes drafted thirty years before. The ethical issues raised by HIV trials are many. The revised guidelines they generated therefore adopted different perspectives but did not always ensure the implementation of their principles.

1.1 RESEARCH AND ETHICS

AIDS AND THE ORGANIZATION OF RESEARCH

During the 20th century, and especially after World War 2, randomization, double blind and placebo control groups became standard methods of medical research. With AIDS, patients' activism has really influenced drug evaluation procedures to speed up access or even the methods themselves. The history of trials has therefore been affected by the HIV epidemic, due to patients' associations questioning certain aspects of trial conduct.

With HIV, for the first time ever, a joint fight against a disease affecting all countries could be contemplated. Research, which concerns vaccines, drug combinations, new drug development or cohort follow up, is conducted simultaneously in several countries, which is problematic. Protocols in developing countries are extensively financed by sponsors from rich countries, with the risk of giving the impression that research is just the exploitation of poor regions for benefits that have nothing to do with them. The Food and Drug Administration (in charge of drug licensing in the United States) reported an increase in the number of studies financed by American sources but carried out elsewhere : 271 in 1990 ; 4 458 in 1999. The AIDS epidemic has therefore also highlighted how dependent developing countries still are on pharmaceutical companies of new products leads the companies to increasingly use Contract Research Organizations (CROs, private sub-contractors) to carry out research. The CROs work faster and outside the usual academic control frameworks as Universities tend to have slower evaluation procedures. In some developed countries, public research centres' private subsidies have decreased to the benefit of CROs. To date for AIDS, in poor countries, there are at least 43 ongoing drug trials and 31 vaccine trials . Research in developing countries on HIV is conducted in a context of increasing trials and privatization of research which may well be detrimental to ethical principles.

THE ETHICAL FRAMEWORK OF RESEARCH

The ethical framework of research is defined in several guidelines. Some have a general outlook, others focus more specifically on experiments in developing countries . Drafted in 1947, the Nuremberg Code is a direct response to nazi physicians' experiments. The Helsinki Declaration, adopted in 1964 by the World Medical Association (WMA) , was revised several times, namely that of October 1975 in Tokyo and that of October 2000 in Edinburgh. It completes the Nuremberg Code and is a reference for subsequent ethical texts guidelines. The recommendations issued by the Council for International Organizations of Medical Sciences (CIOMS) and adopted in 1982 were designed to facilitate application of the Helsinki Declaration in developing countries. They were also revised and endorsed in October 2002.

At various times, other national bodies issued recommendations. In an article published in 1966 in the New England Journal of Medicine, Henry Beecher disclosed ethically objectionable experiments conducted on vulnerable people. The article considerably influenced the evolution of bioethics and the rules applied by researchers . In particular, it generated the Commission that published the Belmont Report in 1978 . In 1993, the French National Advisory Ethics Committee issued a statement on cooperation in biomedical research which proposes to consider it as a North-South partnership . The National Bioethics Advisory Commission (NBAC), set up by the President of the United States in 1995, issued its own report on clinical trials in developing countries in 2001. A year later, in April 2002, the Nuffield Council on Bioethics issued a report on the same topic. At the same time, France's ANRS (National AIDS Research Agency) adopted its Ethics Charter for Research in Developing Countries in May 2002.

THE ACHIEVEMENTS OF BIOETHICS

From these various recommendations emerge the general ethical principles of research conducted on human subjects. As early as 1947, " voluntary " or free and informed consent had been emphasized. In the Belmont Report, the first and foremost principle is " respect for the persons ", based on consideration for subjects' autonomy and the protection of those with limited autonomy. Following this report, several documents put emphasis on research information (aims, methods, expected benefits, potential risks…) and on consent (with information on the freedom to withdraw consent at any time). They also highlighted the importance of evaluation of risks incurred and issued directives on the topic. Furthermore, in 1978, the Belmont Report had devised the " equity principle ": research constraints and risks must not be unduly imposed on certain groups or populations, chosen for their dependence or vulnerablitity, especially if research benefits are intended for other populations. The various guidelines that followed were to put increasing emphasis on that dimension of vulnerability of social groups or entire countries.

As of the 70s, the main procedure for checking the enforcement of principles and for reviewing protocols was the intervention of ethics committees.

1.2 THE DEBATES

THE TRIALS INCRIMINATED

In 1997, various HIV trials were questioned in the New England Journal of Medicine and fuelled many articles and debates. The controversy was based on three sets of trials. The first set, the most controversial, concerned the trials on the reduction of HIV mother-to-child transmission (MTCT) through a shortened course of treatment. Conducted in various countries and with several different treatments, a set of sixteen trials was thought by some commentators to be unethical because of the use of a placebo in the control group when there was an effective treatment, applied in Northern countries. The principle of informed consent was also questioned, for the patients had not always understood, due to translation problems, the meaning of the word placebo.

In 1998, the Vaxgen protocol in Thailand also caused debate. It had been decided that patients who would be infected would be treated with " the best available treatment " and not " the best existing treatment ". The protocol was also ongoing in the United States and the principle of best available treatment was causing inequality between patients in a developed country and patients from a country that could not offer the same treatments.

The third study involved was conducted in the Rakai region of Uganda between 1994 and 1998. The study was evaluating reduction of infection through intake of antibiotics against sexually transmitted diseases in serodiscordant couples. Owing to lack of information on the transmission risks of the virus, investigators' responsibilities to patients infected during the protocol arose.

In all the debates, two different approaches are opposed as to the modalities of clinical trials in developing countries and on their possible regulation. On the one hand, proponents of " universal " ethics consider such practices to be objectionable and existing guidelines insufficient and likely to facilitate the exploitation of vulnerable and third world populations. On the other hand, contenders of pragmatic and contextual ethics consider that health and economic inequalities between countries justify differences in the way trials are designed and conducted. They feel it is more reasonable to adapt to such conditions by experimenting drugs whose chances to be accessed in those countries seem higher.

The main issues raised were therefore the following.

PLACEBO, RISK AND HEALTH CARE LEVEL

Using placebo trials was questioned in all the cases where there existed a proven and applied treatment in developed countries. Proponents of the use of placebo justify it for methodological reasons and consider that the ethical priority is to refrain from exposing populations to a greater risk than the one incurred. Placebo trials are also justified by their short duration and the reduced numbers they require, thus enabling to reach a speedy result and, in theory, to respond to health emergencies in some countries.

CONSENT AND CULTURAL FACTORS

Commonplace problems related to consent (influencing the subject ; comprehending the information document ; possible conflicts of interest) become even more acute when the investigator is from a different culture than the subjects of the study, as the language barrier is a major obstacle, and when the subjects' economic situation makes them more easily vulnerable to exploitation.

Taking the subjects' culture into account sometimes requires specific procedures: oral consent with witnesses can prove more appropriate than written consent, and third-party intervention may be necessary (husband or head of the community). Also, the extent to which the community may benefit from research findings must be defined : village, ethnic group, country.

PROTOCOL EVALUATION AND ETHICS COMMITTEES

In many countries, there are no adequate ethical and scientifical evaluation organizations. Moreover, their existence does not necessarily guarantee their efficiency or independence. Investigators themselves are sometimes members and can get direct benefits from any positive evaluation (publication or appointment to a research team). Beyond the existence of committees and the required training for their members, remains the issue of criteria enabling committees to judge the protocols.

RESPONSIBILITIES AND REDISTRIBUTIVE JUSTICE

The differences in economic, social and cultural situations beteween rich countries and poor countries raise other questions over and beyond the standard principles of research ethics and that fuel the controversy. From a more specific health point of view, poor health care systems and lack of access to care in developing countries are the backdrop to the debates.

Conducting research in the South does have clear advantages: lower research costs, easier recourse to naïve patients. Also, control agencies are more flexible in developing countries and the sponsoring countries' authorities cannot easily carry out evaluations while a trial is being performed. The investigator in a poor country thus has more leeway. Subsequently, opponents emphasize the need for a greater benefit of trial results so as to prevent research from exploiting countries with less strict ethical regulations. Both sponsors and investigators therefore also have a responsibility towards the community within which the trial is being conducted. The community must benefit from research findings : e.g. new available drugs or aquired knowledge.

1.3 REVISED GUIDELINES, NEW PROPOSALS AND LIMITATIONS

The controversy caused the international recommendations to be revised and contributed to the drafting of new ones. These documents emphasize different aspects and sometimes endeavour to solve the problem of the implementation of their proposals.

GUIDELINES FROM INTERNATIONAL ORGANIZATIONS

Revisions of the Helsinki Declaration in October 2000 and of the CIOMS guidelines in October 2002 were fuelled by the work of two international organizations, sometimes open to the representatives of the communities involved. The revised Helsinki Declaration extends the scope of principles to all persons involved in a study and not just to physicians ; it also mentions the precautions to be taken as regards vulnerable subjects liable to undergo pressure. Vulnerability of subjects is a central issue in the CIOMS recommendations and is underlying in three out of four parts of the document : informed consent, vulnerable groups, women participating in research.

Article 29 of the Helsinki Declaration is a response to the placebo controversy. Benefits, risks, constraints and efficiency of a new method must be evaluated by comparison with the best current methods of therapeutic diagnosis or prevention. This does not exclude using placebos in studies where there are no proven methods. Recommendation 11 from CIOMS is similar. The issue of redistributive justice is also tackled in both documents, with CIOMS putting particular emphasis on how research must be consistent with a country's health needs, which is the clear responsibility of sponsor, investigator and ethics committee alike.

PROPOSALS FROM OTHER BODIES

The NBAC and the Nuffield Council have different perspectives in terms of objectives/aims. The NBAC whose mission it is to advise the US government, emphasizes the criteria that are to be respected in order to avoid financing objectionable studies. The consent procedures are lengthily detailed so as to ensure respectful treatment of participants and cultural differences. Conversely the Nuffield Council members tackle all the ethical issues raised by research in developing countries.

Both documents underscore the required participation of representatives of the community in which the trial is being conducted. However, only the Nuffield Council emphasizes how research must take into account the health care priorities of the host country and advocates the reinforcement of health infrastructures.

Guidelines agree on ethics committees' role: they must evaluate the protocols and may admit exemptions to the stipulated proposals. Exemptions endorsed by the ethics committees are also possible as regards the non-involvement of community representatives in protocol design or the availability to participants of theresearch findings.

Among the various guidelines, the ANRS Charter has a special status as it is that of a sponsor who defines its responsibilities and its commitments to participants, investigators and host countries. The Charter establishes the principles of research adapted to the needs of the country where it is being conducted and whereby follow up of patients, once the study is completed, is included in the protocol. Moreover adaptation of the protocol to the cultural specificities, and distribution of benefits must be drafted in collaboration with the community's representatives.

LIMITED IMPLEMENTATION

These guidelines all try to respond to issues raised by research in the South. However, the National AIDS Council considers that their implementation is difficult. The guidelines do not always define whether it is local or foreign ethics committees that validate research projects. Furthermore, while the procedures provided by the various documents may prevent unethical studies, they do accept exceptions to the rules as long as they are justified.

Moreover, conflicts of interest between private research and public health are not mentioned, nor are the ambiguous links beteween scientific journals and private companies.

2 THE NATIONAL AIDS COUNCIL'S RECOMMENDATIONS

Overall, the Council considers that the recommendations issued by the various organizations are good progress. The Council has no wish to rewrite the proposed rules. But it does realize how difficult they are to enforce on the job and acknowledges, in this respect, researchers' feelings about the persistent ethical shortfalls of some studies. The Council therefore wishes to specify what it considers that ethical research should be in the South and to suggest directions that enable to improve implementation.

Developing countries are faced with a great many health challenges that consume their resources and raise the issue of policies to be conducted. The Council must therefore stress, as a prerequisite, that the HIV epidemic is of course its main focus, but related research progression must not be conducted to the detriment of other diseases. The ethical principles stipulated must apply to all research, whether on HIV or not.

2.1 LINKING CLINICAL RESEARCH TO PUBLIC HEALTH

PRINCIPLES

In the guidelines mentioned previously, emphasis is mainly put on the autonomy of the individual person, considered as a central value. It is embodied essentially in the rule of voluntary and informed consent which is the most detailed subject in all the guidelines. The Council is convinced that these principles are essential. Three key points must however be underscored.

Medical research, whether clinical trials, cohort follow up, or social science surveys, does not only concern individuals: it involves societies. Its ethics must therefore necessarily include a collective dimension ; subsequently, the importance of individual autonomy principle must not conceal the equally important principles of justice and solidarity. Inequalities in development and in access to care must be taken into account. They belong to the history of North-South relationships and commit the North to a solidarity duty. The Council feels that a clear definition is needed of the social purpose of research in terms of possible improvement of a community's health, without just considering protocol participants. Any misconduct in this respect is, in fact, an exploitation.

From an ethical standpoint, and while research is being conducted, the question of the person's consent does not come first. It is second to the issue of the relevance and the value of the research at scientific and social level : will it really – directly or indirectly, straight off or later – increase knowledge and/or improve health ? More generally, research ethics cannot just be a matter of procedures to monitor an ongoing protocol. Any research should result in an actual improvement of the health situation in the country or community concerned. At the outstart of any research, it is essential to examine the public health aims, however slight, taken into account by the sponsor, such as expected improvements in terms of personnel training, equipment or availability of research findings.

Taking into account the health issues of the host country by the sponsors and investigators, both public and corporate, must not be limited to the duration of the study. Both get benefits from the research and long term advantages that must be shared with the communities. Their responsibility to participants therefore outlives the study duration. This calls for two comments. First, it does not seem acceptable that after having had access to care during a clinical trial, participants should be offered poorer standards of care after completion of the study. Second, it is essential that on completion, the issue of spin-offs for public health be raised yet again and that any agreement signed at the start, be implemented.

THE SCIENTIFIC COMMUNITY'S RESPONSIBILITY

The various guidelines on research ethics put emphasis on the individual responsibility of research teams towards participants included in the protocol. For the Council, this is a far too restrictive perspective : as the AIDS epidemic stands today, responsibility to the South lies with the entire scientific community and with the large international research organizations. The Council also stresses that in the past, progress in research ethics was made largely thanks to researchers' and organizations' mobilization, both for the drafting of guidelines and anlaysis of how to respect principles in problematic cases. Today, that responsibility is shared by all, whatever outfit, public or corporate, national or international, they belong to. By their daily exchanges, their joint studies or the

organization of scientific meetings, researchers form a real international community. That community must take into account the link between research, access to care and public health. Research policy trends should show evidence of that ambition.

Responsibility however does not only lie with investigators. In particular it must not be forgotten that from the standpoint of principles, ethical requirements also apply to those corporations that contribute to research. Those who benefit from the advantages offered by research in poor countries cannot disregard the extreme poverty of populations and the difficulties that governments face. Nations themselves cannot be exempted from their responsibility.

2.2 HOW TO IMPLEMENT ETHICAL PRINCIPLES

The Council's position is deliberately based on principles. Nevertheless their implementation must be tackled. To date, the only punishment for violation of recommendations and procedures is public reproof, more often than not only in the research community. Likewise, justifying misconduct can only be a satisfactory procedure if exemption is applied for and examined by an informed and punctilious ethics committee and can therefore be rejected. So, in the absence of coercive procedures, ethical principles can only be implemented if there is a strong and sustained volition to do so and if the scientific community, but also various other bodies including the public authorities, are strongly committed.

Implementation will require various means and in particular : ethics committees ; international organizations ; patient associations and NGOs ; scientific journals. The national and international regulation frameworks for research and the pharmaceutical industry can also be useful tools. Awareness of the link between research and public health must be supported in the same way.

ETHICS COMMITTEES

Ethics committees appear to be the main safeguard for the enforcement of the rules established by the guidelines and can guarantee a minimum level of punctiliousness in protocol design. However, cultural problems may arise and evaluation limited to the sponsor's country may prove insufficient. The creation of local ethics committees must be encouraged and supported by organizations that are not linked to the sponsors or investigators of a study. Ethics committees must also be independent from the political authority in their country. Also, various forms of partnership between countries can be promoted.

Furthermore, local committees should not restrict their activity to the preparation of a study but follow it throughout. So as to ensure the implementation of the principles they adhere to, they must actively seek information on the ongoing trials and not just evaluate projects submitted to them. As representatives of civil society, they can contribute to public health policies.

INTERNATIONAL ORGANIZATIONS

The intergovernment organizations participate in the financing of health policies and the internationalization of clinical research. As such, they must be careful not to back any objectionable research. The various modes of intervention at their disposal can enable them to increase awareness on the issue, as UNAIDS did for vaccine research. With the existing guidelines, intergovernment organizations can thus participate in the implementation of ethical principles for research in the South and help create national ethics committees. Although quite different, NGOs can also play that part.

AIDS ASSOCIATIONS

Patient associations in the North must question the methods that enable to develop drugs designed firstly for creditworthy markets. The legitimate participation of patients in the definition of such objectives must not lead research in the South to just be a response to concerns in the North. Associations in developing countries must, to the best of their abilities, monitor research teams' respect of ethical principles. They must also help ensure more transparency in research conducted by private outfits. As is sometimes already the case, associations in the North must support activity of associations in the South and help ethics committees in their work.

REGULATIONS

By using the existing regulations and completing them, the political authorities in the North can facilitate implementation of research ethics in the South.

As regards private companies, criteria for drug licensing must include an ethical dimension and encourage the pharmaceutical industry to consider the respect of principles as an obligation. At the very least, licensing procedures must enable to identify any possible misconduct during development of the product submitted to evaluation.

In a more general way, for research undertaken in France or in Europe, sponsors and investigators respect a regulation framework established by the Public Health Code and a European Directive. That framework can be completed so as to enforce respect of ethical principles in developing countries when research is financed by organizations that are accountable to it.

RESEARCH-SPECIFIC REGULATIONS

Scientific journals' editorial boards must include respect of ethical principles in their criteria for the evaluation of articles submitted for publication. Moreover, a requirement on the link between research and public health should help keep under control repeat projects whose main purpose may be prominence in the research world instead of scientific or health achievements.

THE NEED TO INVOLVE CORPORATE RESEARCH

Although it is a useful support to research and knowledge, the pharmaceutical industry can influence them to a certain extent : it can influence scientific publications - articles or journals –, control medical information to some extent or affect health policies. It is essential to reaffirm that the financial and commercial imperatives of private corporations must in no way be factors to justify a lesser respect for ethical principles and that industry belongs to the research community.

Since the early 1990s, the number of private research projects conducted in developing countries has strongly increased and the committees to which the protocols are submitted do not always meet the requirements endorsed in developed countries. The CROs that fuel the increase are full partners of the pharmaceutical industry. It is therefore advisable that information on their activities in developing countries be accessible and transparent2. Companies which use CRO services must ensure that research carried out on their behalf does not violate ethical principles.

For the past ten years, the International Federation of Pharmaceutical Industries has coordinated the International Harmonization Conference which includes the drug licensing agencies of Europe, Japan and the United States. This work on harmonization of standards applied to those three political entities could include the ethical issues of global research.

CONCLUSION

The increasing internationalization process of medical research means financial flows for projects or scientific exchanges between economically different zones. In such a context, research ethics cannot solely be based on the principle of the person's autonomy. Justice must be a strong principle of ethics serving a transnational solidarity. Subsequently, protocols designed for developing countries must relate to local public health programmes. The international research community is the safeguard of the respect of the principles that also apply to private companies that contribute to research.

Creating ethics committees informed of internationally endorsed standards is a central element for the application of the Helsinki Declaration or CIOMS guidelines. They may have to evaluate protocols that are identical for different countries and, owing to existing cultural differences, it may be advisable for a project to be submitted to different committees. Thus, evaluation in the sponsor's country of origin, in the country where the study will take place or through a partnership between both countries, can be ways to help local committees to be more effective.

Projects can at times be affected by issues that have little to do with scientific research, e.g. financial stakes or academic ambition. To reduce such risks, the powers that be, can contribute to the implementation of these principles. Indeed, mentioning specific issues raised by research in the South in regulation texts, can operate as a firm red flag for the various parties involved. Intragovernment organizations already participate in the implementation process by promoting exchanges and international guidelines. They can be assisted in this monitoring effort by associations and NGOs.

Consequently, the National AIDS Council considers that conducting research in developing countries must take into account the following elements :

Any research must relate to public health objectives of the country in which it is conducted.

Representatives of a country carrying out research in another, less developed, country, must accept the subsequent transnational accountability.

The research community must take collective responsibility for the enforcement of principles emphasized in the various guidelines on research ethics.

Enforcement of recommendations on research ethics in the South must be encouraged by : the research community ; ethics committees ; AIDS associations ; private corporations ; States and regional organizations ; international organizations.

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- Mr Laurent Vidal, anthropologist, Institut de Recherche pour le Développement (April 30th 2002).

1 Position paper on the ARDA trial (altered body fat in HIV positive patients), National AIDS Council, May 15th 2001. Reappraised Statement on the participation of women of child bearing age in pre-vaccine trials supported by the National AIDS Research Agency with HIV negative volunteers, National AIDS Council, April 9th 2002.

2 The Association of Clinical Research Professionals' ethics code seems extremely brief. Studies conducted in developing countries are not mentioned despite their significant growth. The code's text totals fourteen lines (www.acrpnet.org/ethics/index.html). Site visited on February 11th 2003.