The Norwegian National RESEARCH ETHICS COMMITTEES

Medical and health research in low- and middle-income countries

Research ethics guide

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NEM • The National Committee for Medical and Health Research Ethics

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1 INTRODUCTION

Human rights and respect for the individual have become increasingly important since World War II. This is expressed, among other places, in the Universal Declaration of Human Rights, adopted by the UN General Assembly in 1948, and the European Convention on Human Rights (ECHR), adopted by the Council of Europe in 1950.
Respect for the individual, as well as recognition of the need to protect research participants and individual autonomy, have also become more important in research ethics. The Nuremberg Code was drawn up in the aftermath of World War II, based on the Nazis' medical experiments in the concentration camps. It consists of ten points, and is the first international attempt to establish a standard for research ethics in research on humans. In 1964, the World Medical Association adopted the Declaration of Helsinki, which applies for medical research. Among other things, the Declaration of Helsinki has led to a more uniform approach to test subjects across national borders, and also gave rise to independent ethics committees to assess research projects. Norway, as one of only a handful of countries, has a dedicated statute that covers research on humans, personal health data and human biological material. The Health Research Act is based on the Declaration of Helsinki, and applies for medical and health research in Norway, or when research takes place under the auspices of a person or body responsible for the research that has a base in Norway.

Both international and national statutes and regulations thus provide a general framework for research on humans, but do not necessarily encompass all specific issues or situations within research ethics. The need for a broader research ethics approach to research activity in low- and middle-income countries is connected to increased international research activity from the 1980s until today. The growth in the *international health* discipline in Norway has also contributed to this increase, including various study programmes that include field work for students in low-income countries. The research communities acknowledge that the western focus on the individual in research ethics is not adequate for safeguarding research participants in cultural contexts where ideals such as individual freedom and self-determination do not resonate to the same extent.

A broader approach is also connected to the fact that the population in low- and middle-income countries often live under difficult conditions. This limits the latitude that individuals have to act, and can provide an opening for exploitation in relationships with an unequal balance of power. One of the key objectives of the guide is to contribute to prevent exploitation. Setting requirements for research in low- and middle-income countries – that it must be relevant and beneficial for the local community where the research is conducted – is one way to achieve this. Researchers from high-income countries must not conduct research in low-income countries because it is cheaper, or because the research may be easier to carry out. So-called “research tourism” must not occur.

This guide has been prepared to safeguard fundamental principles in medical and health research when the research is conducted in a low- or middle-income country[1].

This guide is intended to aid researchers who are planning to conduct research in low- and middle-income countries, and as an aid in ethical assessment for the Regional Committees for Medical and Health Research Ethics (REC). Various ethical principles are used as a basis for research in low- and middle-income countries. The most important ones are that the research must have local relevance and benefit, that it must be carried out with respect for the research subjects and the community they are a part of, and that the research must benefit the research subjects and their community.

[1] The countries in the world with the greatest number of poor inhabitants, or the highest ratio of poor people in their populations, are in the groups the World Bank classifies as low- and middle-income countries. Report No. 25 to the Storting (2012-2013).

The guide contains recommendations concerning research ethics considerations, advance ethics approval and the mentioned principles. The chapter on advance ethics approval also includes a section of frequently asked questions and answers.

The term “low- and middle-income countries” refers to the World Bank’s term for countries with a low score on gross national product per inhabitant. These countries also score low or very low on three of the UN’s indicators for human development: life expectancy at birth (measure of life expectancy and health status), reading skills for adults (measure of education level) and income (measure of poverty and the degree of access to resources that cover fundamental needs such as clean water, nutrition and medicine).

1.1 TASK FORCE AND REFERENCE GROUP

A task force was appointed in the autumn of 2016 to prepare a research ethics guide for medical and health research in low- and middle-income countries. The assignment was issued by The National Committee for Medical and Health Research Ethics (NEM).

A proposed guide was presented to a broad reference group with diverse competence, most with experience from various global health communities in Norway. The guide was then submitted for consultation to all seven Regional Committees for Medical and Health Research Ethics (REC).

Members of the task force:

Marit Hovdal Moan – senior advisor, PhD ethics, REC Central
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2. RESEARCH ETHICS CONSIDERATIONS

2.1 CULTURAL DIFFERENCES

Safeguarding universal principles of research ethics does not pose a contradiction to showing respect for the cultural context in which the research is conducted. Cultural practices and norms that allow for individual research subjects' interests to be disregarded cannot be legitimised with reference to respecting cultural practices. For example, this could apply to women not being heard, or their consent not being considered relevant. This is in line with the Nuffield Council's report on the ethics of research related to health care in developing countries (1), and the Council for International Organizations of Medical Sciences' (CIOMS) guidelines (2).

In order to ensure respect for culturally contingent norms and values, and simultaneously avoid ethical relativism, the guide uses a set of universal principles and integrates them into a *collective perspective*. In other words, the principles that the guide uses as a basis are formulated both with regard for the protection of individual research participants, and protection of the community they are a part of. This entails an acknowledgement that research participants' interests must be understood and interpreted in context with the society or the community they are a part of (3). An attempt is made to ensure respect for cultural norms and values by angling the principles more in the direction of ethics that protect the community. A review of how the collective perspective is integrated in the guide's basic principles is provided below.

The principle of fairness through local relevance and benefit

From an overall perspective, it is unfair if people in low-income countries are not able to participate in research that may benefit them. Ensuring fair recruitment of research participants on a global scale, a reasonable distribution of benefits and potential burdens of the research among individuals, and taking the community's needs into consideration, will safeguard the principle of fairness. Important issues in this context are whether the research issues are relevant for the society one is researching in and on, and whether the society will benefit from the research. Such a community-oriented understanding of fairness is contingent on involving the community throughout the study, from planning to evaluation. In order to achieve this, the researcher must, as a minimum, enter into collaboration with local researchers and research institutions.

Principle of respect for the people who are the subject of the research, and their community

A community-oriented principle will involve respecting the participants, as part of a community with culturally contingent norms and practices that help shape individuals' identity and perception of themselves, and not only as separate individuals (4). As a result of this principle, the community should be involved in the information and consent process. The process should ensure that the potential subjects can confer with their families or others in the community – if they wish – before they potentially consent to participate in the research.

Principle that the research must benefit and not harm the research participants and their community

A community-oriented principle of charity and avoiding harm includes an assessment of whether a research project may benefit or harm the community, in addition to the individual research participants. For example, a research project might be a direct advantage for a society in that participation results in the population gaining access to medicine, and more directly in that the local research infrastructure is reinforced. A project can harm the community if the results have a stigmatising or offensive effect for the group (5)(10).

2.2 RISK OF EXPLOITATION

A fundamental principle in medical and health research ethics is that "the consideration for the participants' well-being and integrity shall take precedence over the interests of science and society". This protects the research participant from exploitation. Exploitation can be interpreted as "situations where one party uses the other solely as a means for serving their own interests and objectives", and thereby reducing the other person to an object, without consideration for the person's inherent dignity.

An important premise in international and national guidelines and guides aimed at medical and health research in low or middle-income countries is that the potential for exploiting the research participants and their local communities is greater in such a context than in a high-income setting. This heightened risk of exploitation could be due to the living conditions of the population, little or no developed public health services, a low percentage of people who can read and write, and/or limited or no developed infrastructure for evaluation and verification of research projects. These factors can make groups and individuals vulnerable to exploitation in that the benefits of the research fall to societies and individuals in entirely different parts of the world than the one being researched. The classic example in this context is pharmaceutical studies in low-income countries where the drug will not be available to the study population or the local community after the study ends, and where the benefits from the research mainly end up serving patients in high-income countries.

The guide recommends that researchers return the result of the research to the research participants and their local communities. And the research must also be beneficial for the local community over the longer term, for example by expanding the capacity of local research institutions, contributing to training or further education of health personnel, or other measures that can bolster local research capacity and/or health infrastructure (6)(7)(8)(9). This can prevent exploitation, and eventually help reduce the inhabitants' social vulnerability.

2.3 VULNERABLE GROUPS

Populations in a low or middle-income setting are considered to be more vulnerable to exploitation in connection with medical and health research than populations in a high-income setting. The term "vulnerable" is used here in the sense of "social vulnerability", which is a form of vulnerability associated with resource poverty. Low or no income, combined with little or no education and limited access to resources to meet basic needs, such as clean water and medicines, can curtail a person's ability to make informed and independent choices, both in general, but perhaps particularly in a research context.

In a western cultural setting, vulnerability is often associated with a physical condition (such as a disability, substance dependency, mental or somatic illness), or a stage of human development (child, youth, elderly). Social vulnerability can be linked to these forms of vulnerability, but not necessarily.

Ethnic and religious affiliation, gender and sexual identity can also make individuals socially vulnerable. For example, the comments on CIOMS guideline 18 (2) emphasise that, in many societies, women are considered to be particularly socially vulnerable in a research context: "They can, to a greater extent, be subject to negligence or harm due to submission to authorities, reluctance to ask

questions, and a cultural tendency to tolerate pain [..] Women will also be more exposed to increased psychological, social and physical risk, for example as a result of participation in research on partner violence".

Vulnerability is linked to individual people, not necessarily entire population groups. Social vulnerability as a consequence of resource poverty entails vulnerability at a group level, but it affects individuals differently, and can have an impact in combination with other vulnerability factors. As an example, a young woman who is poor, who cannot read or write, and who is part of a patriarchal society, could be more vulnerable to exploitation or harm than an older man in the same society.

Researchers are unable to change the economic and social factors that underlie social vulnerability over the short term. Nevertheless, researchers have an obligation to give an account of potential negative effects a research project might have on the participants and local communities. Together with local partners, the researcher also has a duty to draw up an action plan to reduce potential negative effects of the research project. The research must also contribute to value creation that, in time, can contribute to making the research participants and the local community less socially vulnerable. The requirement for local relevance and benefit is one way to achieve this.

2.4 LOCAL PARTNERSHIP

"Collaborative partnership" and "community engagement" are two terms that are frequently used in international guidelines to emphasise the importance of ensuring that a research project is firmly anchored in, and cognizant of, local conditions and needs. The established Norwegian expression "user participation" highlights the similarities with Norwegian realities, although "local partnership" entails a broader involvement of the research participants and their community. The revised version of CIOMS guideline no. 7 with comments contains a requirement for community engagement in the planning and study design phase, in the recruitment and consent phase, and in the dissemination phase (2). A summary of CIOMS' comments on this recommendation follows below.

The basis for CIOMS' guideline on local partnership is that involvement of the research participants in all phases of a research project shows respect for the participants and the society they are a part of. The risk of exploitation can be minimised by involving research participants in the choice of issues that are the subject of research. Local authorities' prioritised areas of commitment within health can be a good starting point for a dialogue on which research issues are considered to be useful for the local society, but researchers should listen to potential participants and their communities, as well as other persons or institutions that could be affected by implementation of the project and its result.

Early involvement through local partnership is also a step in ensuring that relevant participants understand the objective of the research project, what participation will entail for them in terms of disadvantages and risk, that participation is voluntary, and that they can withdraw without any negative consequences. Local partnership also builds trust, contributes to mutual learning between participants and researchers, lends insight into local norms and customs which is valuable in a recruitment and consent process, and gives the population a sense of ownership to the research they take part in.

As a first step in establishing local partnerships, the researcher should cooperate with local researchers associated with local research institutions or clinics. Where relevant, the researcher should also involve representatives of the group or the local community they will be researching. There are multiple ways to do this, for example by starting a dialogue with a local council of elders or with other leadership figures in advance of the project. Options include establishing an advisory committee consisting of local resource persons (community advisory board / community assemblies) to provide input on the research issues' relevance for the community (10), and/or involving local

health care professionals (11) or other local resource persons (community owned research persons) in the information and recruitment process (12).

The relevance of involving representatives of a local community, in addition to local researchers, can vary. Weijer and Emanuel's placement of various forms of communities on a scale from "extremely connected" to "loose" (5) can serve as a starting point for this assessment. It is likely that the more connected the community, the more the population and their representatives should be involved in the research process. For example, an indigenous population with a representative council with political authority to make binding decisions on behalf of the group, is considered to be extremely connected. A village with a representative council of elders, and a shared perception of health, can largely be considered to be connected.

A few examples bear mentioning; "if a community is to give input regarding the content of a protocol, it must have spokespersons who can speak on behalf of the community. If one is to seek consent from the community for permission to obtain individual consents from its members, it must have a legitimate political authority that can make binding decisions on behalf of the community. If the community is to consent to future use of biological material, there must also be a shared perception of health, in addition to a common political authority (13).

Regardless of which form of cooperation is chosen, it is essential for the legitimacy of the process that dialogue groups have a broad composition. Where local researcher groups, community leaders or local resource persons are exclusively made up of men, the researchers have a duty to include women in a dialogue group or establish separate fora where the perspective of women and girls concerning the research project and the research issues can be heard. It is particularly important to devote attention to diversity in the reference group when the research is being done in relation to marginalised persons, minorities or persons with illnesses associated with significant stigma, such as HIV.

In this context, it is important to be aware of power structures that a dialogue group or involvement of local resource persons could help to strengthen. Persons with high status within a community could gain increased status and influence as a consequence of being listened to by researchers who come from outside the community. Such a dynamic can cause other members of the community to feel pressured to take part in the research project, or not be heard regarding which research issues they believe should be prioritised.

3. ETHICAL PRE-APPROVAL

3.1 WHEN NORWEGIAN PRE-APPROVAL MUST BE SOUGHT

Requires Norwegian REC approval

- Norwegian research owner
- Norwegian sponsor
- Association with Norwegian research institution
- Research as part of an education programme abroad, funded by a Norwegian research institution/sponsor

Does NOT require Norwegian REC approval

- Research projects with anonymous data
- Analyses of biological materials that are not interpreted in Norway, and without a Norwegian person or body responsible for the research
- Counselling or consultation regarding organisation, scientific design, etc.

Section 3 of the Health Research Act states that the Act applies for "research conducted on Norwegian territory or when research is conducted under the auspices of a person or body established in Norway which is responsible for the research ".

This means that, as regards research in low- and middle-income countries where a person or body responsible for the research institution, or potentially the sponsor, is established in Norway, pre-approval from REC will be required. This requirement applies regardless of whether Norwegian or foreign researchers are participating in the project.

If there is any doubt as to whether the project requires pre-approval from REC, the project manager should submit a presentation assessment to REC. REC will then be able to assess whether an application should be submitted.

3.1.1 Requirement for local ethical approval if Norwegian REC approval is required

When REC approves a project, they generally require the project to obtain a local research ethics assessment. This emerges from the guide for committee members prepared by the Council of Europe's Steering Committee on Bioethics.

"As with other externally funded multinational research, the research ethics assessment shall take place in the host countries, as well as in the sponsor's country. Local assessment is particularly important in order to determine whether the research is ethically acceptable in relation to the customs and traditions in the affected community" (14, p. 48-51)".

The requirement for both Norwegian REC approval and local research ethics approval is also in line with CIOMS' guidelines (2), and UNESCO's Universal Declaration on Bioethics and Human Rights (13).

However, there is no requirement that local approval must be secured before the Norwegian REC can assess the application. It is sufficient that local approval is stipulated as a criterion for approval, and that a copy of the local approval is sent to the Norwegian REC before the project is initiated.

In some instances, the implementation of a research project will be incompatible with protecting the participants' welfare and integrity, due to the risk of harm. Regardless of what the local research ethics assessment in the host country should be, it will then be unacceptable from a research ethics perspective to give pre-approval for the project pursuant to the Health Research Act. In other words, there is no compromising the principle of always prioritising the participants' rights ahead of research interests; see also NEM's resolution of 2011/215.

When questions of research ethics are raised, e.g. concerning the method of recruitment, compensating participants or obtaining consent, there will be greater latitude for a discretionary assessment by the Norwegian REC. One should consider whether the requirements in the Health Research Act can be harmonised with assessments undertaken where the project will be conducted. The discretionary assessment must nevertheless be exercised within the framework of the Health Research Act.

Frequently asked questions and answers

Do we have to apply for pre- approval from the Norwegian REC when master's students or PhD research fellows associated with a Norwegian institution are added to a project that has been approved in the country it is being conducted, and where data acquisition has already started?

Answer: If a master's student or PhD research fellow is associated with a Norwegian research institution, they must apply to REC for approval of the part of the project they will be carrying out. If the project originates from a Norwegian research institution, he or she can apply for an amendment of the main project. If the project originates from a foreign research institution, they will have to apply to REC for approval of their part of the research project as a separate project. If data has already been collected, and the master's student or PhD research fellow will contribute to the analysis of this data, REC will ask to see the original consent document, to assess whether the analyses the master's student or PhD research fellow will perform are covered by the original consent.

➢

Do we have to apply to the Norwegian REC if master's students or PhD research fellows from other countries, but who are associated with a Norwegian institution, will be using already collected de-identified data from their home country?

Answer: If the master's student or PhD research fellow is associated with a Norwegian research institution, they must apply to the Norwegian REC for pre-approval of their project. Among the factors the REC will assess are whether re-use of the already collected data is covered by the original consent.

➢

A foreign research fellow is enrolled in a PhD programme associated with both a Norwegian and a foreign research institution, and will receive a degree from both universities. Does the research fellow have to apply for approval from the Norwegian REC?

Answer: If the foreign research fellow is associated with both the Norwegian and the foreign institution, and/or the Norwegian institution is contributing funding for the degree, they must apply for approval from the Norwegian REC.

➢

A project is planned and funded by researchers abroad. The project manager is a Norwegian professor who is involved as an advisor to a research fellow who takes part in the project. Does the project need approval from the Norwegian REC?

If the project manager is associated with a Norwegian research institution, pre-approval must be sought from the Norwegian REC.

➢

A study is being planned abroad. Biological material will be collected for microbiological testing. The material will also be sent to Norway for analyses. Does the project need approval from the Norwegian REC?

Answer: If researchers/research staff associated with a Norwegian institution will be participating in the project, an application must be sent to the Norwegian REC. If a Norwegian laboratory will only be used to analyse the samples, which are then destructed or sent back, no application to the Norwegian REC is needed.

➢

A Norwegian company is planning to conduct genetic analyses to identify the risk of e.g. Alzheimer's disease. The biological material was collected in another project and has received ethics approval in the country in which the samples were collected. The participants have consented to participation, as well as to the collection of the biological material. No Norwegian research participants will be recruited. The biological material will be brought to Norway in de-identified form.
Is the project subject to application in Norway, and is there a need to establish a new, specific research biobank in Norway for storage of the imported biological material?

Answer: As long as a Norwegian company is planning/funding the project, an application for pre-approval from the Norwegian REC will be needed in this case. The question as to whether a research biobank must be established, and whether this requires Norwegian pre-approval, must be determined following a concrete assessment. One factor here will be how long the human biological material will be stored in Norway.

➢

A study is being planned abroad where the research participants will be children under the age of 16. Pursuant to Norwegian law, the consent of both parents will then be required. However, for practical and cultural reasons, it will be difficult to secure the father's consent in this connection. The mother will usually be the primary care provider, and the father will be away from the home due to work. Can a deviation be made from the main rule of consent from both parents in such cases?

As a point of departure, deviations cannot be made from the provisions of the Health Research Act. The issue of consent from both parents was addressed in appeal case 2018/348.

The assessment of this project placed decisive emphasis on the fact that the research was closely related to treatment, where there are different rules for consent. NEM determined that, in this concrete project, the mother's consent was sufficient. In the ethical assessment, NEM also emphasised that the concrete project was considered directly beneficial for the individual child taking part in the project, as well as for other new-borns in low-income countries. The participation also entailed no disadvantage for the research participants, but rather an opportunity for treatment. The project was properly organised and had already secured local ethics approval. The local approval did not require consent from both parents. If the requirement for consent from both parents was upheld, the project most likely could not be conducted due to the difficulty in obtaining consent from the father. NEM also referred to the fact that, in connection with research in low- and middle-income countries, it is important to exercise cultural sensitivity by adapting to and respecting local cultural circumstances when this is possible.

➢

A registry study is planned in a low- and middle-income country. Master's students at a Norwegian educational institution will participate as project staff. The project will not have access to identifiers, and the information will be anonymous for them. Do they need to send an application to REC?

In this instance, the information will not be anonymous as long as the registry owner has an identifier. The project therefore requires pre-approval from REC.

If the information is truly anonymous, it is not considered to be personal health data, and research projects on anonymous information do not require pre-approval from REC. This means that it will be important to ensure that the information is truly anonymous; it must not be possible, either directly or indirectly, to trace the information back to the person who gave the information. It will therefore not always be adequate to remove identifiers, names, national ID numbers or other personally identifying characteristics. More about when information is considered anonymous can be found in recital 26 of the preamble to the EU's General Data Protection Regulation (GDPR).

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4. FAIRNESS, RESPECT AND DOING GOOD

4.1. FAIRNESS - RESEARCH MUST HAVE VALUE FOR THE COMMUNITY BEING RESEARCHED

Summary

Local benefit and relevance, defined as a response to health needs or priorities in the group on which the research will be conducted, are generally independent of the nature of the project. The researcher must substantiate the relevance of and benefit for the local community vis-à-vis REC.

Local benefit and relevance are determined in dialogue with the local partner. Partnership with local researchers linked to a local research institution is a minimum requirement.

Where relevant, one should also involve representatives from the group or the local community on which research will be conducted, in addition to local researchers. Cooperation is established in the planning phase and maintained throughout the entire research process.

The researcher must document local partnership vis-à-vis REC. Where involvement of other local resource persons beyond local researchers is not relevant, this must be substantiated vis-à-vis REC.

The researcher must substantiate vis-à-vis REC why the project will be carried out in a low or middle-income setting and explain why it cannot be carried out in a high-income setting.

Local relevance means that the research project has a positive value for the subjects of the research, or those from whom data is collected. However, benefit is a broad term, and it is not sufficient that the research participants are paid for their participation, e.g. with a free health exam or other types of rewards. It is the purpose of the project that must contribute to health-related benefit locally, and in a long-term perspective. The benefit concept is best understood together with the relevance concept, in that the project must address a relevant problem for the local community where the research takes place, and where the result of the research will be beneficial for the involved parties over the long term. Long-term benefit could, for example, entail building local research expertise and infrastructure.

Projects that do not have any value for the group being researched, either in the present or the future, entail an exploitation of the persons who have contributed their data. A requirement for local relevance can be considered a form of fairness in that those who contribute their data should also be able to expect something in return. Local health-related relevance was particularly emphasised in the most recent revisions of the Declaration of Helsinki and CIOMS' recommended comments in the chapter on research in a low-income setting (2). CIOMS' guideline and Article 20 of the Declaration of Helsinki explicitly state that health-related relevance – defined as "responsive to health needs or priorities of the communities or populations where the research will be conducted" - is a criterion for projects that will be conducted in, or will obtain data from, a low or middle-income setting, to be

considered ethically responsible. Articles 15, 17 and 21.3 of UNESCO's Universal Declaration on Bioethics and Human Rights (14) and the Council of Europe's guidelines for REC members (Regional Ethics Committees) express the same principle in Chapter 9b (14).

A core issue in this context is whether the project has health relevance for the group or the local community where the research is conducted, or the country in which the research is conducted. This should be clarified in dialogue with local partners.

In the application to REC, the project manager must document local partnership, give an account of the project's local health relevance, and also present a plan for returning the knowledge to the local community.

4.2. RESPECT – RESEARCH SHALL BE BASED ON RESPECT FOR THE INDIVIDUAL AND THE COMMUNITY

4.2.1. Special considerations for information and involvement in the project

Summary

Information strategy is planned in collaboration with the local research partner.

Women and representatives from relevant minority groups must be involved in the preparation.

Consent to participate in research must be informed and voluntary.

Information should be communicated in a local language where words, terms and illustrations are culturally and linguistically tailored to the target group.

A plan for communicating information must be presented to REC.

An information strategy should be developed which explains what is being communicated, in what manner and through which channels. The strategy should be developed in collaboration with the local research partner. Resource persons in the local community should be involved in the effort where relevant.

Women and representatives from relevant minority groups must be involved in drawing up the information strategy, if necessary, via dedicated fora.

In research ethics, informed and voluntary consent from research participants is the key to respecting the research participant as a unique individual. In a low or middle-income setting, the lack of reading and writing skills, language, and frame of reference, as well as a value system that differs from the researcher's, can challenge the established western perception of how to best achieve informed consent. Key concepts or terms in medical and health research are not necessarily known in the culture in which the research will be taking place. Many words and expressions cannot be translated. For example, the local language may lack equivalent words for terms such as randomisation, placebo,

genotyping, control group, saturation, etc. Translation of the names of illnesses can result in use of words surrounding the illness that are perceived as disparaging or stigmatising in the local language. In the same vein, terms such as risk, health and illness may differ from how we use them in Norway (15)(16).

Local partners should be involved in ensuring that potential participants understand the goal of the research project, and what participation will entail for them as regards any disadvantages and risk.

A plan for communicating information to the local community and to the individual participant, must be presented to the REC.

4.2.2. Recruitment and collective involvement

Summary

The recruitment process shall be prepared in cooperation with local partners, i.e. local researchers as a minimum, and where relevant, representatives for the group or the community on which research will be conducted.

The researcher should involve women in the preparation of the information brochures/recruitment process to safeguard the rights of women and girls in the implementation of a research project.

Need for, or requirement for consultation in advance of consent must be respected but does not replace the requirement for individual consent.

Other persons than the researcher should recruit research participants when local norms indicate that researchers that come from the outside shall be treated as guests, which may give rise to special obligations.

Compensation to the participants should be clarified in dialogue with the local ethical committee and local partner. It must not be of such value as to induce potential participants to consent to participate in the research against their better judgement.

The established perception of how one can best achieve *voluntary and informed consent* without interference from others, and without the use of force or bribery, is challenged by a more collectivist understanding of the individual as part of a community. A too strict interpretation of the requirement for *individual* consent can be difficult or impossible to fulfil in a context where a western understanding of autonomy is not dominant (17). In line with the most recent revisions of CIOMS' guidelines (2) and the Declaration of Helsinki, this guide presumes that respect is compatible with a decision to seek advice from the community the potential participants identify with. These could be heads of families, spouses, religious leaders, or councils of elders. The need for, or requirement for, such consultation should be respected. The consent that is granted following such a process of

consultation shall, however, be the individual's own, and based on the research participant's own desire to participate.

The voluntary consent can also be challenged by various forms of hierarchical systems, which require potential research participants to consult persons of authority, such as spouses, a council of elders, bearers of traditional knowledge, or health personnel, before decisions are made. Factors such as age, gender, education level and social class all affect the degree to which individuals have the perception that they can make an independent decision to take part in a research project. This issue is more acute where local customs indicate that the researcher must ask local leaders or councils for permission to initiate a research project. Local resource persons can have the benefit of great respect, and they can exert influence on the individual's decisions.

The guide also assumes that local partnership is important to safeguard the individual research participant, while at the same time respecting the person who is part of the community. Given the respect and confidence that is placed with leaders, traditional bearers of knowledge and health personnel, the research group should involve such resource persons in the project at the earliest possible stage, so that, through dialogue, a common understanding can be gained of where the boundaries for the community's involvement in the decision process should be placed. Cooperation with local resource persons should be evaluated throughout the project period, and the message that participation is voluntary, and that participants can withdraw without suffering negative consequences, must be communicated repeatedly to the participants throughout the research process.

An adjacent issue relates to local customs that indicate that researchers that come from the outside shall be treated as guests, which triggers special obligations. In cases where the research group understands that this is the case, the researcher should not be directly involved in recruiting the participants.

4.2.3. The therapeutic misconception

Participating in research can entail an element of treatment or therapy. Some research participants misunderstand the main intention of the research project. They might think that research is treatment, and that being allowed to take part in a (clinical) study, means they could become more well, or achieve better general health. This is often called "the therapeutic misconception". In research ethics in western countries, avoiding this misconception has been regarded as important to prevent people from choosing to participate in research based on the wrong premises, which could be regarded as violating the principle of voluntary participation. This is particularly important in cases where interventions can entail risk, and where the prospects of any direct benefit for the participant seem to be entirely absent. Good information brochures and consent routines are often mentioned as measures to guarantee that research participants know what they are agreeing to.

The therapeutic misconception can be challenging to accommodate in a low or middle-income setting. It apparently presumes a premise that often is not present in these settings, namely that treatment is something that others (a public health service) handle. In countries where the general health care services are extremely limited, even minimal health follow-up in a research project may seem to be far more and better treatment than one could otherwise have access to. At the same time, the absence of health follow-up services for people who are the subject of research could emerge as being outright exploitation of citizens in poor countries. Therefore, this principle can be turned upside down. Researchers must understand that participating in a research project in a low or middle-income setting often both *can and should* appear as being in the participants' own interest, if the research is to call itself ethical and responsible. If research participation *does not* emerge as being useful for the individual participant, the follow-up, preparedness and treatment in a project will have to aim for such a low level of care that the research will appear to be unethical. A minimum position

that says that research is okay as long as no one is worse off from participating, has set the ethical threshold too low (7).

4.2.4. Compensation

Summary

Research participants should receive reasonable reimbursement for costs directly incurred during the research, such as travel costs, and receive reasonable compensation for their inconvenience and time spent, either as monetary compensation, goods or services.

Reimbursement or compensation must not be of such value as to induce potential participants to consent to participate in the research against their better judgement ("undue inducement").

The researcher shall consult with a local research ethics committee to clarify acceptable reimbursement or compensation for research participants.

The researcher shall establish vis-à-vis the Norwegian REC that the level of compensation is reasonable.

Compensation for participation in research can induce persons to take part against their better judgement, and thus undermine the principle that participation in research shall be voluntary. Here the guide applies CIOMS' thirteenth recommendation on reimbursement and compensation to research participants (2). In the same manner as in a high-income setting, research participants in a low or middle-income setting "shall be reasonably reimbursed for costs directly incurred in connection with participation in the research project, such as travel expenses, and shall receive reasonable compensation for inconvenience and time spent, either in the form of money, goods or services." What is considered "reasonable" must be viewed in the context of local monetary value, and local customs.

It is important to be aware of the social and economic context. Economically disadvantaged people will be more motivated to take higher risk based on financial compensation. Therefore, remuneration must never be compensation for risk. In projects with low risk, the researcher should be aware that there could be a greater risk of inducing someone to incur risk or discomfort on behalf of others.

4.2.5. Documentation of consent

Summary

Written documentation of consent is one of several ways of documenting consent.

Fingerprints can take the place of signatures if the participant cannot read or write, and shall be certified by signature of an independent third party.

In cases where written documentation by signature or fingerprint is not possible or desirable, verbal consent must be obtained.

Verbal consent must be documented, in writing or in some other manner (video, audio file), and shall be certified by the signature of an independent third party

As a general rule, consent shall be documented in writing by the research participant signing a consent form. However, there will be cases where documentation of consent by signature is not possible or appropriate. This applies if those asked to participate cannot read or write. It also applies in those cases where the requested participants can read and write, but where, for various reasons, they do not want to sign a document. As pointed out in the Nuffield report (18), signing a formal document may be associated with negative consequences (loss of property, taxation, legal action), or expose the participants to risk. As an example of the latter, the report refers to a study of violence in close relationships. Obtaining written consent from the women who participated in the study was considered to be inappropriate, as collecting signatures was equated with creating a registry of women exposed to domestic violence. In turn, this could contribute to exposing the women to an increased risk of harm. One way to solve this problem is to obtain verbal consent with witnesses.

The guide also recommends that, when written consent with signature or fingerprint is not possible, or is considered inappropriate, then consent shall be given verbally. Documentation of consent can then take place by audio recording. Verbal consent and consent by fingerprint must be verified by at least one independent witness, by means of signature.

4.3 DOING GOOD – DO NOT HARM TO THE PARTICIPANTS OR THE COMMUNITY

4.3.1. Minimum standard of care

Summary

The minimum standard of care for the control group in a clinical study shall never be lower than the best available level in the country's public health service.

The standard of care *should as a rule* be equivalent to the best possible in the world.

The level must be clarified in consultation with local researchers/partners, and shall be justified vis-à-vis the REC.

A plan for safeguarding the participants' health needs during and after the study shall be submitted to the REC.

All health and medical research in low-income countries must deal with the challenge that it is not possible to "refer" the participants to a well-functioning public health service when they need help. In high-income countries, a well-functioning public health service is more taken for granted and contributes to a natural division of labour between the research community and the health service. The absence of such a background must be offset in one way or another.

Researchers in low-income countries have care and treatment obligations that deal with *reciprocity* in research. In high-income countries, the attitude is that reciprocity is fulfilled in that the research contributes to better treatment options, and that the participants who need it, can always be referred to a treatment option outside the research project and the researchers' obligations. In low-income countries, the participants do not automatically receive anything back from their own health service, and the researchers must compensate for that by ensuring an ethically acceptable standard of care associated with the project. What is deemed to be an acceptable standard of care is a subject of discussion, particularly in connection with clinical studies, and in those cases where the researcher discovers other illness in the participant than what is the subject of the research.

The debate on reasonable standard of care has particularly focussed on the services to control groups in clinical research. The debate surrounding standard of care arose in the wake of 15 clinical studies carried out in low- and middle-income countries in the 1990s, to examine the possibility of reducing HIV transmission between mother and foetus/child, and where the control group received a placebo instead of a standard treatment. Standard treatment had routinely been administered since 1994, e.g. in the US. The studies created intense debate between those who believed it was unethical to allow use of a placebo when a standard treatment existed, and those who defended the use of placebos in clinical research in low-income countries, on the premise that standard treatment is often not available from a financial standpoint and cannot be administered in a prescribed manner in any event due to lack of infrastructure (19).

This guide assumes that, if one wishes to research the effect of a new drug, patients in the control group should, as a point of departure, receive the best treatment in the world. In line with the Nuffield Council's report on ethical health research in developing countries, however, the guide allows for deviating from this principle, for example if the best treatment is not available in the

specific country because it is too costly, or administration of the best treatment available in the world is not possible due to lack of health infrastructure (1). Then it may be more appropriate to compare the new treatment with the one that is available in the relevant community. The report also states that the standard of care must be defined in consultation with service providers, and substantiated vis-à-vis a research ethics committee (1).

This is also included in the most recent revision of CIOMS' recommendation on research carried out in a low-income setting (2). If such a reasoning is to be ethically prudent, it must also be reasonable to expect that if the new treatment proves to be more effective, then it must also be accessible, in terms of price, in the low-income country. Otherwise, it would also be perceived as if populations in low-income countries are used purely as vehicles for pharmaceutical research in high-income countries.

4.3.2. Safeguarding participants' health needs during and after the study

An adjacent problem is the question of the researcher's and the research's treatment obligations vis-à-vis research participants if, as part of an intervention, one discovers a different illness than the one being researched. It may seem unreasonable that western researchers must be obligated to offer treatment and care at a level corresponding to the home country's health service when, strictly speaking, they do not have a treatment relationship to the participants. This could also contribute to potential participants largely perceiving a research project as a treatment service, e.g. with the consequence that a potential risk is underestimated (20).

The guidelines from Nuffield Council of Bioethics suggest that the best available treatment in the national health service should be the baseline if the participants develop a different type of illness than the one being researched (9). The project manager should prepare a plan for how to handle any unforeseen findings as a result of the research.

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