ACRP Regulatory Affairs Committee Review (RAC) of CIOMS Draft Revised Ethical Guidelines

CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects

What is the guidance?
The CIOMS Working Group formed to review and update the 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects as a result of evolutions in the fields of biomedical research and research ethics.

Who does it impact & how?
When the document is finalized, the CIOMS International Ethical Guidelines may impact the conduct of clinical research and research ethics oversight internationally. CIOMS is affiliated with the International Conference on Harmonisation (ICH), the International Council for Science (ICSU), International Federation of Pharmaceutical Manufacturers Associations (IFPMA), MedDRA Maintenance and Support Services Organization (MSSO), the World Health Organization (WHO), UNESCO, and the United Nations. Research conducted in accordance with any of the affiliations' guidance or regulations may also be impacted by changes to the CIOMS Ethical Guidelines.

What did ACRP's RAC have to say about it?
The RAC review team provided comments on many of the 25 guidelines. See all comments attached. Some specific examples of comments include the following:

- Disagreement that research ethics committees must compare risks in research with those that an average, normal, healthy individual experiences in daily life.
- Disagreement with a guideline statement that resulting data may not be published in certain circumstances.
- Request for clarification on where the agreements on who will finance, deliver and monitor care and treatment will be documented and what the ethics committee's role is in reviewing this information, with a caution provided that ethics committees are often not equipped to judge the adequacy of such arrangements.
- Request for clarification on what an appropriate "pre-determined interval" would be, as it's being recommended that researchers must ensure at pre-determined intervals that each participant is willing to continue study participation, even if there are no changes in the design or objectives of research.
- Disagreement with the recommendation that subjects who are withdrawn from a study for health-related reasons be compensated as if full study participation had taken place.

When were the RAC's comments sent to the agency?
March 1, 2016

Where can I access this document?
http://www.cioms.ch/index.php/guidelines-test

Revision of CIOMS 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects

Guideline 1 – Social value		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
78-82	**The Guideline states:** Additionally, they must ensure that all research personnel are qualified by virtue of their education and experience to perform competently in their roles. This includes receiving appropriate ethics education and training. These considerations must be adequately addressed in the research protocol or other materials for submission to the research ethics committee (Appendix I).	Please clarify what considerations must be adequately addressed in the protocol or other materials for submission to the research ethics committee. Training considerations are not included in the research protocol or in materials for EC submission. Appendix 1 does not list this type of documentation being expected in the protocol, this should be reconciled.

Guideline 2 – Research conducted in low-resource settings		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
130-159	**Commentary on Guideline 2**	**We request additional guidance on this requirement. Specifically:** Where/how is responsiveness documented? Who decides if the documentation is adequate? The IEC?

Guideline 3 – Equitable distribution of benefits and burdens in the selection of groups of participants in research		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
226-229	**The Guideline rightly describes the results of injustices of the past for pregnant or reproductive capable women as well as children, but as currently stated does not address age.** **The guideline currently states:** In general, equitable distribution requires that participants be drawn from the qualifying population in the general geographic area of the study without regard to race, ethnicity, economic status or gender unless there is a sound ethical or scientific reason to do otherwise.	We request an addition of AGE in the discussion related to equitable distribution.

Guideline 4 – Potential benefits and risks of research		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
364	**Minor typographical error. Currently reads:** especially when adequate safeguards to protect confidentiality are "no" in place	Should read **NOT** in place, instead of "no" in place.
440-442	**The Guideline states:** **"**Research ethics committees must be similarly vigilant about not permitting greater research risks in populations of patients who routinely undergo risky treatments or diagnostic procedures (for example cancer patients). Rather, risks in research must be compared to risks that an average, normal, healthy individual experiences in daily life or during routine examinations.	**This requirement seems to defy the concept of respect for persons** (Belmont Report "To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others"). Individuals with seriously debilitating, life threatening diseases do not make most of their life decisions from the context of a "normal, healthy individual". They should not be evaluated against this standard for their willingness to take greater risks. Otherwise, IECs/IRBs/RECs, which historically have often behaved paternalistically, may usurp the right of the compos mentis persons who have been fully informed of potential risks and benefits (including the potential for no benefit or even harms of research participation) to make an informed, autonomous choice about which risks they are willing or unwilling to assume.
469-470	The concern about stigmatizing groups or contributing to discrimination of those groups does not seem well served by non-disclosure of research results. **The Guideline states** "……and to the need to publish the resulting data in a manner that is respectful of the interests of all concerned or in certain circumstances not to publish the findings."	**Suggest elimination of the last part of this sentence "or in certain circumstances not to publish the findings".** The requirement to publish "in a manner that is respectful of the interests of all concerned" should be safeguard enough to ensure limiting stigmatization or discrimination. In an age of ever increasing transparency, we believe there are greater risks associated with failure to publish research results, so long as appropriate measures are taken to minimize potential

		harms to individuals or groups.

Guideline 5 – Choice of control in clinical trials		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 6 – Caring for participants' health needs		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
781	**The Guideline states:** Agreements on who will finance, deliver, and monitor care and treatment must be documented.	**Request clarification:** Where would this be documented? At the research site; in the protocol? If the Ethics Committee is expected to be responsible for assessing the adequacy, we respectfully submit that research ethics committees are not constituted nor equipped to judge the adequacy of such arrangements, at least not without very clear guidance from regulatory authorities.

Guideline 7 – Community engagement		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
863-866	**The Guideline states:** Moreover, and to the extent possible, researchers must support experiments by patients or other individuals in order to ensure that any gathered data meet appropriate scientific standards, and that experiments are conducted in an ethically acceptable manner.	**This does not seem in any way feasible. We request clarification**. Perhaps some examples would be helpful, including a rationale for each example. In addition there is no description of sources and uses of funds to support and monitor such research, nor who may be eligible.

Guideline 8 – Collaborative partnership and capacity building for research and review		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 9 – Individual informed consent		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
954-956	**The Guideline states:** In long-term studies, researchers must ensure at pre-determined intervals that each participant is willing to continue study participation, even if there are no changes in the design or objectives of the research.	**Please provide guidance on what an appropriate "pre-determined interval" may be.**

Guideline 10 – Modifications and waivers of informed consent		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 11 – Use of stored biological materials and related data		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
	We commend promotion of the concept of "informed opt-out".	

Guideline 12 – Use of health-related data in research		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
1352-1354	**The guideline states:** When researchers use coded health-related data, the key to the code must remain with the custodian of the biobank. **AND** Researchers are only allowed to use anonymized or coded health-related data. The key to the code must remain with the custodian of the databank.	**This seems redundant and perhaps one of these sentences is meant to be deleted?**

Guideline 13 – Reimbursement and compensation for research participants		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
1552-1555	**The Guideline states:** *"Compensation after study withdrawal.* When a researcher withdraws a participant from a study on health-related grounds, the person must be compensated as if full study participation had taken place. If the withdrawal is due to a research-related harm, this harm must be treated and the participant is entitled to additional compensation…" Requiring compensation for study activities NOT performed because it may be detrimental to the health of the subject to do so seems unreasonable. They should be compensated for their participation only unless there has been research-related harm.	***Suggest revision as follows:*** *Compensation after study withdrawal.* When a researcher withdraws a participant from a study on health-related grounds, the person must be compensated for study participation up to the point of such withdrawal. *When a subject is withdrawn from a study due to a research-related harm, this harm must be treated and the participant is entitled to additional compensation."*

Guideline 14 – Treatment and compensation for research-related harms		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 15 – Research involving vulnerable persons		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 16 – Research involving individuals who are not capable of giving informed consent		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 17 – Research involving children and adolescents		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 18 – Women as research participants		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 19 – Pregnant women and lactating women as research participants		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 20 – Research in disaster situations		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 21 – Implementation research		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 22 – Use of online information		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 23 – Research ethics committees and review		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 24 – Public accountability		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
2656-2659	**The Guideline states:** Researchers have a duty to make the results of their health-related research publicly available and are accountable for the completeness and accuracy of their reports. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. This seems to directly contradict part of Guideline 4 (lines 469-470).	**Request that these discrepancies be harmonized.**

Guideline 25 – Conflicts of interest		
Text Line	**General Comments**	**Specific Comments/Suggestions for Modifications**
No Comments		

Guideline 1: Social value

The ethical justification of health-related research involving humans is its social value: the prospect of generating the knowledge and/or the means necessary to protect and promote people's health. Clinicians, researchers, policy makers, public health officials, patients, pharmaceutical companies and others rely on the results of research for activities and decisions that impact individual and public health, welfare, and the use of limited resources. Therefore, researchers, regulators, research ethics committees, and sponsors must ensure that proposed studies are scientifically sound, build on an adequate prior knowledge-base, and are likely to generate valuable information. Such research must always be carried out in ways that uphold human rights, and respect, protect, and are fair to study participants and the communities in which the research is conducted.

Commentary on Guideline 1

General considerations. In order to be ethically permissible, health-related research with humans, including research with identifiable human tissue or data, must have social value. The social value of this research is ultimately grounded in the quality of the information that it produces, its relevance to significant health problems, and its contribution to the creation or evaluation of interventions, policies, or practices that promote individual and public health. It is essential to the social value of health-related research that its design is scientifically sound and that it offers a means of developing information not otherwise obtainable. For example, so-called “seeding trials” violate this requirement if their purpose is to influence clinicians who participate in the study to prescribe a new medication rather than to produce knowledge about the merits of these interventions.

Sponsors, researchers, and research ethics committees must ensure that these conditions related to social value are met and that the methods to be used are appropriate for the objectives of the research and the field of study. Additionally, they must ensure that all research personnel are qualified by virtue of their education and experience to perform competently in their roles. This includes receiving appropriate ethics education and training. These considerations must be adequately addressed in the research protocol or other materials for submission to the research ethics committee (Appendix I).

Scientific rigor. The requirement of scientific rigor applies to all health-related research with humans, regardless of funding source or degree of risk to participants. In part, this is because a diverse range of stakeholders (including clinicians, researchers, policy makers, patients, pharmaceutical companies and others) rely on the information that research generates to make decisions that have important consequences for individual and public health. For example, the evidence produced in early-phase research provides the foundation for subsequent studies and methodological shortcomings can derail promising avenues of research and squander valuable resources. Many other forms of research, such as clinical trials, health-systems research, epidemiological studies or post-marketing studies, generate data that is relevant for clinical decision-making, health and social policy, or resource allocation. Independent of the risks such studies pose to participants, ensuring that studies uphold high standards for scientific quality is essential for maintaining the integrity of the research enterprise and its ability to fulfill its social function.

Social value and other requirements for health-related research with humans. Although the social value of research is a necessary condition of ethical permissibility, it is not sufficient on its own. Rather, all research with humans must be carried out in ways that show respect and concern for the rights and welfare of individual participants and the communities in which research is carried out. This respect and concern is manifest in requirements for informed consent, ensuring that risks are minimized and are reasonable in light of the importance of the research, and other requirements

discussed in this document. Research must also be sensitive to issues of justice and fairness. This concern is manifest in requirements governing whose health needs are investigated; how risks, burdens, and likely benefits of individual studies are distributed; and access to the knowledge and interventions that result from such inquiry. These and other ethical aspects of research are discussed in the remaining guidelines and their commentaries. The research protocol submitted for ethical review must include, when relevant, the items specified in Appendix I, and must be carefully followed in conducting the research.

Dissemination of results of research and review of research. The importance of disseminating scientific information, including negative findings, is discussed in Guideline 24. Scientific review is discussed further in the Commentary to Guideline 2: *Research ethics committees* and *Ethical review.*

Guideline 2: Research conducted in low-resource settings

Before instituting a plan to undertake research in a population or community with limited resources or infrastructure, the sponsor, researchers, and relevant public health authority must ensure that the research is responsive to the health needs or priorities of the communities or populations where the research will be conducted.

As part of their obligation, sponsors, researchers must also:

- **Make every effort in cooperation with government and civil society to make available as soon as possible any intervention or product developed, and/or knowledge generated, for the population or community in which the research is carried out. This requirement does not preclude capacity building or the provision of additional benefits to the population or community;**

- **Consult with and inform communities about the plans for making any intervention or product developed intervention available, including the responsibilities of all relevant stakeholders.**

Commentary on Guideline 2

Responsiveness of research to health needs or priorities. The responsiveness requirement can be met by demonstrating that research is needed to provide new knowledge about the best means of addressing a medical condition present in that community or region. Where communities or policy makers have determined that research on particular health needs constitutes a public health priority, studies that address such needs seek to provide social value to the community or population and are therefore responsive to their health needs. Concerns about responsiveness might hinge on the relevance to the community of the information a study is designed to produce. For example, a question about responsiveness might arise if a study of a new intervention is planned for a community in which established effective interventions for a medical condition are not locally available and the new intervention has features that would make it difficult to implement in that community. In such cases, researchers and sponsors must consider whether the study could be made more relevant to local health needs or must be conducted elsewhere. If the knowledge gained from the research is used primarily for the benefit of other populations, the responsiveness requirement is violated and the research raises serious concerns about justice, which requires a fair distribution of the benefits and burdens of research (see guideline 10 on equitable distribution).

Responsibilities and plans. When the research has important potential benefits to the population or community, the responsibility to make any intervention or product developed available to this population is shared among researchers, sponsors, governments, and civil society. For this reason, the negotiation among stakeholders must include representatives in the community or country, including, where appropriate, the national government, the health ministry, local health authorities, relevant scientific and ethics groups, as well as members of the communities from which subjects are drawn, and non-governmental organizations such as health advocacy groups. The negotiation must address the health-care infrastructure required for safe and appropriate use of any intervention or product developed, the likelihood and conditions of authorization for distribution, and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, when such information is not proprietary. A plan to ensure the availability and distribution of successful products can require engaging with international organizations, donor governments and bilateral agencies, civil society organizations, and the private sector. In resource-poor settings, the development of the local health-care infrastructure must be facilitated at the outset so that it can be of use during and beyond the conduct of the research

Post-trial availability for communities and populations. Even if research addresses a question that has social value for the community or population where it is carried out, the community or population will not benefit from successful research unless the knowledge and interventions that it produces are made available to the population. This is of particular concern for research conducted in low-resource settings where governments can lack the means or infrastructure to make such products widely available.

An investigational drug is unlikely to be generally available to the community or population until sometime after the conclusion of the study, as it may be in short supply, and in most cases could not be made generally available before a drug regulatory authority has approved it. However, other successful outcomes of research that do not require approval by a regulatory agency must be implemented as soon as feasible. An example is the introduction of male circumcision in countries with a high burden of HIV disease. Research has demonstrated a significant preventive effect of male circumcision, following which programs to offer male circumcision were introduced in several countries.

When the outcome is scientific knowledge rather than a commercial product, complex planning or negotiation among relevant stakeholders may not be needed. There must be assurance, however, that the scientific knowledge gained will be distributed and available for the benefit of the population. One example might be a study to find out why a medical condition--such as neural tube defects --is prevalent in a particular population. Another example could be the fact that fruit bats and bush meat are a source of the Ebola virus. Such knowledge, when introduced into community education programs, can be used to educate the population about foods to eat or avoid in order to promote or maintain health.

The requirements regarding post-trial availability for communities and populations must not be construed as precluding studies designed to evaluate novel therapeutic concepts. As a rare exception, for example, research may be designed to obtain preliminary evidence that a drug or a class of drugs has a beneficial effect in the treatment of a disease that occurs only in regions with limited resources, when the research could not be carried out reasonably well in more developed communities. Such preliminary research may be justified ethically even if there will not be a specific product that could be made available to the population of the host country or community at the conclusion of the preliminary phase of its development. If the concept is found to be valid, subsequent phases of the research could result in a product that could be made reasonably available at its conclusion.

Additional benefits to the population or community. Additional benefits may accrue to the community or population, especially in resource-poor settings. Such benefits can include improving the health infrastructure, training laboratory personnel, and educating the public about the nature of research and the benefits resulting from a particular study. Whereas capacity building must be a part of any research conducted in low-resource settings, other types of benefits will depend on the circumstances of the research and environment in which it is carried out. These additional benefits must be determined in consultation with the communities or the local population. Additional benefits may also include considerations that research or research partnerships can contribute to the overall scientific environment of such countries and communities

Community engagement. From the beginning of research planning, it is important to engage in consultations with communities who will participate in the study. This consultation must be an open, collaborative process that involves a wide variety of participants, including community advisory boards, community representatives, and members of the population from which research participants will be recruited. Active community involvement helps to ensure the ethical and scientific quality and outcome of proposed research. In addition, it promotes smooth study functioning, contributes to the community's capacity to understand the research process, enables members to raise questions or concerns, and helps to build trust between the community and researchers (see guideline 5 Community engagement).

Guideline 3: Equitable distribution of benefits and burdens in the selection of groups of participants in research

Sponsors, researchers, governmental authorities, and research ethics committees must ensure that the benefits and burdens of research are equitably distributed. Groups and communities that are invited to participate in research must be selected for scientific reasons and not because they are easy to recruit given their compromised social or economic position or their ease of manipulability. Because exclusion from research can result in or exacerbate health disparities, the exclusion of groups in need of special protection must be justified. Groups that are unlikely to benefit from the knowledge to be gained in the research must not bear a disproportionate share of the risks and burdens of research participation.

Commentary on Guideline 3

General considerations: The equitable distribution of benefits and burdens in the selection of study populations requires that the benefits of research be distributed fairly and that no group or class of persons bear more than its fair share of the risks or burdens from research participation. When benefits or burdens of research are to be apportioned unequally among individuals or groups of persons, the criteria for unequal distribution should be morally justifiable and not arbitrary. In other words, unequal allocation must not be inequitable. In general, equitable distribution requires that participants be drawn from the qualifying population in the general geographic area of the study without regard to race, ethnicity, economic status or gender unless there is a sound ethical or scientific reason to do otherwise. For example, in cases where the underrepresentation of particular groups results in or perpetuates health disparities, equity may require special efforts to include members of those populations in research (see guidelines 17, 18 and 19).

Fair distribution of research benefits. Equity in the distribution of the benefits of research requires that research is not disproportionately focused on the health needs of a limited class of people, but instead aims to address diverse health needs across different classes or groups of persons. In the past, groups of vulnerable persons were excluded from participation in research because this was

considered the most expedient way of protecting these groups (for example children, women of reproductive age, pregnant women). As a consequence of such exclusions, information about the diagnosis, prevention and treatment of diseases in such groups of persons is now limited. This has resulted in a serious injustice. If information about the management of diseases is considered a benefit that is distributed within a society, it is unjust to deprive groups of persons of that benefit. The need to redress these injustices by encouraging the participation of previously excluded groups in basic and applied biomedical research is widely recognized.

Fair distribution of research burdens. Research with human participants typically requires that some persons or groups undertake risks and burdens in order to generate the knowledge and/or the means necessary to protect and promote people's health (see guideline 1). Equity in the distribution of burdens of research requires that special care be given to ensure that individuals, communities or populations that are already disadvantaged or marginalized are not overrepresented in research and that groups or communities who participate in research are likely to benefit from future applications of the knowledge produced. The selective reliance on disadvantaged or convenient populations is morally problematic for several reasons. First, it is unjust to selectively ask poor or marginalized individuals or groups to participate in research because this concentrates the risks and burdens of research on people who already experience increased risks and burdens from social and economic disadvantage. Second, these individuals and groups are also the most likely to be excluded from, or to have difficulty accessing, the benefits of research. Third, the broad inclusion of different social groups in research helps to ensure that research is conducted in a socially and ethically acceptable manner. When research is concentrated in disadvantaged or marginalized groups, it may be easier to expose participants to unreasonable risks or undignified treatment.

In the past, certain groups of persons have been overused as research subjects. In some cases such overuse has been based on the administrative availability of the populations. For example, in the United States, prisoners were considered ideal subjects for Phase I drug studies in the past because of their highly regimented lives and, in many cases, their conditions of economic deprivation. Other populations that may be overrepresented in research because of their easy administrative availability include students in researchers' classes, residents of long-term care facilities and subordinate members of hierarchical institutions. In other cases, impoverished groups have been overused because of their willingness to serve as subjects in exchange for relatively small stipends, because of their desire to access medical care, or because research hospitals are often located in places where members of the lowest socioeconomic classes reside.

Not only may certain groups within a society be inappropriately overused as research participants, but also entire communities or societies may be overused. Such overuse is especially questionable when the populations or communities concerned bear the burdens of participation in research but are unlikely to enjoy the benefits of new knowledge and products developed as a result of the research.

(See Guideline 2: *Research in populations and communities with limited resources.)*

Guideline 4: Potential benefits and risks of research

To justify imposing any risks on participants in health research, the research must have social value. Before inviting potential participants to join a study, the researcher, sponsor and the research ethics committee must ensure that risks to participants are minimized and

appropriately balanced in relation to the prospect of individual benefit or the social value of the research.

It is essential not to directly judge the risks and potential benefits of studies as a whole in order to avoid missing potential concerns about individual interventions. Rather, the risks and potential benefits of each individual research intervention or procedure in the study must first be evaluated. Then, in a second step, the aggregate risks and potential benefits of the entire study must be assessed and must be considered appropriate.

- **For research interventions or procedures that have the potential to benefit participants, risks are acceptable if they are outweighed by the prospect of individual benefit and the available evidence suggests that the intervention will be at least as advantageous, in the light of foreseeable risks and benefits, as any established effective alternative. Therefore, as a general rule, participants in the control group of a trial must receive an established effective intervention. The conditions under which placebo may be used are spelled out in guideline 5.**

- **For research interventions or procedures that offer no potential benefits to participants, the risks must be appropriate in relation to the social value of the knowledge to be gained (expected benefits to society from the generalizable knowledge).**
- **In general, when it is not possible or feasible to obtain the informed consent of participants, research interventions or procedures that offer no potential benefits must pose no more than minimal risks. However, a research ethics committee may permit a minor increase above minimal risk when it is not possible to gather the necessary data in another population or in a less risky or burdensome manner, and the social value of the research is compelling (see Guidelines 16 and 17).**

- **The aggregate risks of all research interventions or procedures in a study must be considered appropriate in light of the potential benefits to participants and the social value of the research.**

The researcher, sponsor and research ethics committee must also consider risks to groups and populations, including strategies to minimize these risks.

Commentary on guideline 4

Ethical Grounding. Participants in health research are often exposed to a variety of interventions or procedures, many of which pose some risk. In this guideline, the term “intervention” is used to refer to those entities that are the object of study, such as new or established therapies, diagnostic tests, preventive measures and various techniques (for example financial incentives) that might be used to modify health behavior. The term “procedures” is used to refer to research activities that are performed in order to describe the object of study, for example the safety and efficacy of a new therapy. Procedures include surveys or questionnaires, clinical exams, monitoring (for example an electrocardiogram), blood draws, biopsies, imaging procedures, as well as the use of methods and techniques for conducting the research, such as random, weighted, or other methods to assign participants to various interventions in order to answer research questions.

Many research interventions and procedures pose some risks to participants. Risk is generally understood as an estimation of two factors: first, how likely it is that a participant will experience a physical, psychological, social or other harm and second, the magnitude or significance of the resulting harm or burden. The ethical justification for exposing participants to risks is the social value

of research, namely the prospect of generating the knowledge and the means necessary to protect and promote people's health (see guideline 1). However, there may be risks that cannot be justified, even when the research has great social value and competent adults would give their voluntary and informed consent to participate in the study. For example, a study that involves deliberately infecting healthy individuals with Anthrax or Ebola—both of which pose a very high mortality risk due to the absence of specific treatments—would not be acceptable even if it could result in developing an effective vaccine against these diseases. Therefore, researchers, sponsors, and research ethics committees must ensure that the risks to which participants are exposed in a study are appropriately balanced in relation to the social value of the research, and that the study does not exceed absolute upper risk limits in the given study population. What constitutes an appropriate risk-benefit ratio cannot be expressed in a mathematical formula or algorithm. Rather, it is a judgment that results from a careful assessment and reasonable balancing of a study's risks and potential benefits. This judgment must reflect fair consideration to the rights and interests of everyone affected by a study.

Evaluation of individual research interventions and procedures. To evaluate the risks and potential benefits of a research study, researchers, sponsors, and research ethics committees must first evaluate the risks and potential benefits of each individual research intervention and procedure and then judge the aggregate risks and potential benefits of the study as a whole. Taking these successive steps is important because global judgments of the risk-benefit profile of a study as a whole may miss concerns raised by individual interventions within the study, and they are more likely to be inaccurate. For example, a study may involve research procedures that do not pose significant risks, yet the procedures fail to yield important and non-duplicative information. Global risk-benefit judgments would likely miss this concern. By contrast, scrutiny of each individual research intervention and procedure in the study would result in removing the duplicative procedures and thereby minimize risks to participants.

Potential benefits. Research has a range of potential benefits. For future patients, it generates the knowledge and the means necessary to protect and promote their health (the so-called "social value" of research; see guideline 1). For study participants, research can offer potential clinical benefits from study interventions or from being included in the study and receiving, for example, high-quality clinical care as part of the research. A study intervention offers a prospect of clinical benefit when previous studies provide credible evidence that the intervention's potential clinical benefits will outweigh its risks. For example, many investigational drugs in Phase III trials offer a prospect of individual benefit. Researchers, sponsors and research ethics committees must maximize the potential benefits of studies for both future patients and study participants. For instance, the social value of studies can be maximized by making data or specimen available for future research (confer guideline 24). Potential clinical benefits to participants can be maximized by targeting populations who stand to benefit most from the intervention under study. Measures to maximize potential benefits need to be carefully balanced with competing considerations. For example, sharing data or specimen for future research can pose risks to participants, especially when adequate safeguards to protect confidentiality are no in place.

Risks to research participants. To evaluate the acceptability of risks in a given study, researchers, sponsors and research ethics committees must begin by ensuring that the study poses a socially valuable research question and employs sound scientific methods for addressing this question. They must then determine for each intervention and procedure in the study that the associated risks to participants are minimized and that mitigation procedures are in place. This can involve ensuring that plans and procedures exist to adequately manage and reduce risks, for example by:

- providing pathways for responding to adverse events
- ensuring safety monitoring by establishing a Data Safety and Monitoring Committee (DSMC)
- instituting clear criteria for stopping a study
- installing safeguards to protect the confidentiality of sensitive personal data

- providing exemptions for researchers from requirements to disclose or report information about illegal activities of study participants (such as engaging in prostitution in countries where it is forbidden by law)
- avoiding unnecessary procedures (for example by performing laboratory tests on existing blood materials instead of drawing new blood, where scientifically appropriate)
- excluding participants who are at a significantly increased risk of being harmed from an intervention or procedure.

Measures to minimize risks need to be carefully balanced with competing considerations regarding the social value of research and fair subject selection. For example, decisions to stop a trial due to early, significant findings have to be balanced with the need to collect robust data on investigational interventions that are adequate to guide clinical practice.

Researchers, sponsors and research ethics committees must then ensure that the risks of each intervention and procedure, once minimized, are appropriately balanced in relation to the intervention's prospect of benefit for the individual participant or the social value of the research. For interventions that have a prospect of individual benefit, risks are acceptable if they are outweighed by the potential benefits for the individual participant *and* the intervention's risk-benefit profile is at least as advantageous as any established effective alternative. Participants in the control group of a clinical trial must be provided with an established effective intervention; exceptions to this general rule are set out and discussed in guideline 5.

Judgments about the risk-benefit profile of study interventions, and how it compares to the risk-benefit profile of any established alternatives, must be based on the available evidence. Therefore, researchers and sponsors have an obligation to provide, in the research protocol, a comprehensive and balanced overview of the available evidence that is relevant for evaluating the risks and potential benefits of the research. In research protocols for clinical trials, researchers and sponsors must clearly describe results from preclinical studies and, where applicable, early phase or exploratory trials involving human subjects or the study intervention, and relevantly similar interventions. They must also note any limitations of the available data as well as any disagreement about the foreseeable risks and potential benefits, including potential conflicts of interests that might influence conflicting opinions. Judgments that a research intervention has a favorable risk-benefit ratio that is at least as advantageous as any established alternatives must be supported by a credible interpretation of the available evidence.

There is widespread agreement that it is ethically permissible to administer an intervention to a participant when that intervention has a favorable risk-benefit profile and is at least as advantageous as any established effective alternative. However, there is ongoing disagreement as to whether it is permissible for researchers to withhold, delay or withdraw established effective interventions for research purposes or to use interventions that are less effective than established alternatives. Again, guideline 5 offers more specific guidance on these provisions.

Finally, researchers, sponsors and research ethics committees must ensure that the aggregate risks of all research interventions or procedures in a study are acceptable. For example, a study may involve numerous interventions or procedures that each pose limited risks, but these risks may add up to an overall significant level of risk that is no longer acceptable in relation to the social value of the study. To guard against this possibility, researchers, sponsors and research ethics committees must complete risk-benefit evaluations with an overall judgment about the risks and potential benefits of the given study.

The minimal-risk standard. In studies where the participants' informed consent is not possible or feasible to obtain (see Guidelines 10, 16, 17), research procedures that have no prospect of individual benefit should pose no more than minimal risks. The minimal-risk standard is often defined by comparing the probability and the magnitude of harms that are anticipated from research procedures

without the prospect of individual benefit with the probability and magnitude of harms that are ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The intent of these comparisons is to determine the level of acceptable research risk by analogy with the risks of activities in other areas of life: when the risks of an activity are considered acceptable for the population in question, and the activity is relevantly similar to participating in research, then the same level of risk should be considered acceptable in the research context. These comparisons typically imply that research risks are minimal when the risk of serious harm is very unlikely and the potential harms associated with more common adverse events are small.

One difficulty with these risk comparisons, however, is that different populations can experience dramatic differences in the risks of daily life or in routine clinical examinations and testing. Such differences in background risk can stem from inequalities in health, wealth, social status, or social determinants of health. Therefore, research ethics committees must be careful not to make such comparisons in ways that permit participants or groups of participants from being exposed to greater risk in research merely because they are poor, members of disadvantaged groups or because their environment exposes them to greater risks in their daily lives (for example poor road safety). Research ethics committees must be similarly vigilant about not permitting greater research risks in populations of patients who routinely undergo risky treatments or diagnostic procedures (for example cancer patients). Rather, risks in research must be compared to risks that an average, normal, healthy individual experiences in daily life or during routine examinations. Furthermore, risk comparisons must not be made to activities that pose unacceptable risks themselves, or in which people choose to participate because of the associated benefits (some sporting activities, for example, are thrilling precisely because they involve an elevated risk of harm).

When the risks of a research procedure are judged to be minimal, there is no requirement for special protective measures apart from those generally required for all research involving members of the particular class of persons.

Minor increase above minimal risk. When a research procedure is judged to pose greater than minimal risks and the informed consent of study participants is not possible or feasible to obtain, the research ethics committees must find: 1) that the risks of the research procedure only constitute a minor increase over minimal; 2) that it is not possible to gather the data in another population or in a less risky or burdensome manner; and 3) that the research has sufficiently compelling social value to justify exposing participants to the increased risk. While there is no precise definition of a "minor increase" above minimal risk, the increment in risk must only be a fraction above the minimal risk threshold and considered acceptable by a reasonable person. It is imperative that judgments about a minor increase above minimal risk pay careful attention to context. Thus, research ethics committees need to determine the meaning of a minor increase above minimal risk in light of the particular aspects of the given study.

Risks to groups. In order to achieve the social value of research, results must be made public (see guideline 24). However, research results in certain fields (for example epidemiology, genetics, sociology) may present risks to the interests of communities, societies, or racially or ethnically defined groups. For example, results could indicate – rightly or wrongly – that a group has a higher than average prevalence of alcoholism, mental illness or sexually transmitted disease, or that it is particularly susceptible to certain genetic disorders. Publishing such results could therefore stigmatize a group or expose its members to discrimination. Plans to conduct similar research should be sensitive to these considerations, to the need to maintain confidentiality during and after the study, and to the need to publish the resulting data in a manner that is respectful of the interests of all concerned or in certain circumstances not to publish the findings.

Similarly, conducting research studies may displace or disrupt local health infrastructure and thereby pose risks to the community. The research ethics committee must ensure, as part of evaluating the

risks and potential benefits of research studies, that the interests of all who may be affected are given due consideration. Sometimes it may be advisable to supplement the study participants' informed consent by community consultation (see guideline 7, Community Engagement). In assessing the risks and potential benefits that a study presents to a population, it is appropriate to consider the potential harm that could result from forgoing the research or from failing to publish the results.

Minimizing risks to groups. Participation in certain research projects (such as HIV or abortion studies) may impose upon the research subjects significant risks of social discrimination or harm; such risks merit consideration equal to that given to adverse medical consequences of experimental drugs and vaccines. Efforts must be made to reduce their likelihood and severity. For example, participants in vaccine trials must be enabled to demonstrate that their HIV-seropositivity is most likely due to their having been vaccinated rather than to natural infection. This may be accomplished by providing them with documents attesting to their participation in vaccine trials, or by maintaining a confidential register of trial participants, from which information can be made available to outside agencies at a participant's request.
(See also guidelines 1: *Social value*; 5: *Choice of control*; 10: *Waivers of consent*); 15 *Vulnerable* persons; 16: *Incompetents* 17: *Children.)*

Guideline 5: Choice of control in clinical trials

As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention.

Placebo may be used as a comparator when there is no established effective intervention for the condition under study, or when placebo is added on to an established effective intervention.

When there is an established effective intervention placebo may be used as a comparator without providing the established effective intervention to participants only if

- **there are compelling scientific reasons for using placebo; *and***
- **delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures.**

Risks and benefits of other study interventions and procedures must be evaluated according to the criteria set out in guideline 4.

Commentary on Guideline 5

General considerations for controlled clinical trials. The conduct of controlled clinical trials is methodologically essential in order to test the relative merits of investigational interventions. To obtain valid results in a controlled trial, researchers must compare the effects of an experimental intervention on participants assigned to the investigational arm (or arms) of a trial with the effects that a control intervention produces in subjects drawn from the same population. Randomization is the preferred method for assigning participants to the arms of controlled trials. Assignment to treatment arms by randomization tends to produce study groups comparable with respect to factors that might influence study outcomes, removes researcher bias in the allocation of participants, and helps to ensure that the study results reflect the effects of administered interventions and not the influence of extraneous

517 factors.

Although randomised controlled clinical trials are often considered the gold standard, other study designs can also yield valid research results. Researchers and sponsors must carefully consider whether the research question can be answered with an alternative design, and whether the risk-benefit profile of alternative designs is more favorable when compared to a trial that includes a placebo arm.

The use of placebo controls in clinical trials creates the potential for conflict between the demands of sound science and the obligation to safeguard the health and welfare of study participants. In general, studies must be designed to generate sound scientific information without delaying or withholding established effective interventions from participants. Researchers and sponsors may deviate from this default rule when withholding such interventions is methodologically necessary and exposes participants to no more than a minor increase above minimal risk.

Established effective intervention. An established effective intervention for the condition under study exists when it is part of the medical professional standard. The professional standard includes, but is not limited to the best proven intervention for treating, diagnosing or preventing the given condition. In addition, the professional standard includes interventions that may not be the very best when compared to available alternatives, but are nonetheless professionally recognized as a reasonable option (for example as evidenced in treatment guidelines).

Yet established effective interventions may need further testing, in particular when their merits are subject to reasonable disagreement among medical professionals and other knowledgeable persons. Clinical trials may be warranted in this case, in particular if the efficacy of an intervention or procedure has not been determined in rigorous clinical trials. Another example is that sometimes well-conducted trials have been performed but the risk-benefit profile of a treatment is not clearly favorable, such that patients might reasonably forgo the intervention for the given condition (for example antibiotic treatment for otitis media in children, or arthroscopic knee surgery). When there are several established effective interventions but it remains unknown which treatment works best for whom, comparative effectiveness research may help to further determine the effectiveness of an intervention or procedure. This may include testing an established effective intervention against a placebo, provided the conditions of this guideline are met.

Some contend that it is not acceptable for researchers to ever withhold or withdraw established interventions. Others argue that this may be acceptable, provided the risks of withholding established interventions are necessary in order to ensure that the results are interpretable and valid. The present guidelines take a middle stance on this issue. They set a default to test potential new interventions against an established effective intervention. When researchers propose to deviate from this default, they require that researchers give a compelling methodological justification and the risks from withholding or withdrawing the established intervention are no greater than a minor increase above minimal risk.

Placebo. An inert substance or sham procedure that is provided to patients with the aim of making it appear to participants (and possibly others, such as the researchers themselves) that they are receiving an active intervention for their condition. Placebo interventions are methodological tools used with the goal of isolating the clinical effects of the drug or intervention under study, in that they allow researchers to treat participants in the study arm and the control arm of a trial in exactly the same way, except that the study group receives an active substance and the control group does not. The clinical effects observed following the administration of a placebo can be both beneficial and harmful. The risks of the placebo intervention itself are typically very low (for example ingestion of a "sugar pill").

In some disciplines, such as surgery and anesthesia, testing the effectiveness of interventions requires the use of sham interventions. For example, the participants in the active arm of a surgery trial may receive arthroscopic surgery on their knee while participants in the control group may receive only a minor skin incision. In other cases, both groups may receive in invasive procedure, as when a catheter is inserted into a patient's artery and thread into the heart participants in the active arm but stopped short of the heart in patients in the control arm. The risks of sham procedures can be

considerable (for example surgical incision under general anesthesia) and must be carefully considered by a research ethics committee.

Placebo controls. The use of placebo is uncontroversial in the absence of an established effective intervention. As a general rule, when an established effective intervention exists for the condition under investigation, study participants must receive that intervention within the trial. This is does not preclude comparing the effects of potential new interventions against a placebo control, as all participants receive the established effective intervention and are then randomised to the investigational intervention or placebo. For example, add-on designs are common in oncology where new chemotherapeutic agents are often used in combination with established treatments.

Alternatively, when there is credible uncertainty about the superiority of an established effective intervention over an investigational agent, it may be permissible to compare the effects of an investigational intervention directly against an established effective intervention. In each of these cases, the study design safeguards the welfare of participants by ensuring that they are not deprived of care or prevention that is believed to be an effective response to their health needs.

Compelling scientific reasons. Compelling scientific reasons for placebo controls exist if the trial cannot distinguish effective from ineffective interventions without a placebo control (sometimes referred to as "assay sensitivity"). Examples for "compelling scientific reasons" include the following: the clinical response to the established effective intervention is highly variable; the symptoms of the condition under study fluctuate and/or there is a high rate of spontaneous remission; or the condition under study is known to have a high placebo response. In these situations it can be difficult to determine without a placebo control whether the experimental intervention is effective, as the condition may be improving on its own (spontaneous remission) or the observed clinical response may be due to a placebo effect. For example, many trials of anti-depressants use placebo controls because patients with depression often have waxing and waning symptoms, and depressive symptoms are known to have a high placebo response.

When a researcher invokes compelling scientific reasons to justify the use of placebo, the research ethics committee should seek expert opinion, if this opinion is not already present in the research ethics committee itself, as to whether use of an established effective intervention in the control arm would invalidate the results of the research.

Minimizing risks to participants. Even when placebo is justified on one of the bases set forth in the guideline, the possibly harmful effect of receiving this comparator must be minimized consistent with the general requirements to minimize the risks of research interventions (guideline 6). In the context of placebo-controlled trials this can imply the following.

First, researchers must decrease the period of placebo use to the shortest possible that is consistent with achieving the scientific aims of the study. Risks in the placebo arm may be further reduced by permitting a change to active treatment ("escape treatment").

Second, as discussed in guideline 4 commentary, the researcher minimizes harmful effects of placebo-control studies by providing for safety monitoring of research data.

Minimal risks of receiving placebo. Risks of receiving placebo count as minimal when the likelihood of serious harm is very low and the potential harms with more common adverse events are low, as described in guideline 4. This implies for example that, when the investigative intervention is aimed at a relatively trivial condition, such as the common cold in an otherwise healthy person or hair loss, and using a placebo for the duration of a trial would deprive control subjects of only minor benefits, the

risks of using a placebo-control design are minimal. The risks of receiving placebo in the presence of an established effective intervention must be compared with the risks that an average, normal, healthy individual experiences in daily life or during routine examinations.

Minor increase above minimal risk. Consistent with guideline 4, the minor increase above minimal risk standard also applies to placebo-controlled trials. Although there is no precise definition of a "minor increase" above minimal risk but the increment in risk must only be a fraction above the minimal risk threshold and considered acceptable by a reasonable person. It is imperative that judgments about a minor increase above minimal risk pay careful attention to context. Thus, research ethics committees need to determine the meaning of a minor increase above minimal risk in light of the particular aspects of the given study.

Placebo control in a different population. In some cases an established effective intervention is available but the existing data may have been established under conditions that are substantially different from local health care norms (for example a different route of administration for drugs). In this situation, a placebo-controlled trial can be the best way of evaluating the intervention as long as this trial is responsive to local health needs, as set out in guideline 2), and all other requirements in these guidelines are met.

Placebo control in a population with limited resources when established effective intervention cannot be made available for economic or logistic reasons. In some cases, an established effective intervention for the condition under study exists, but for economic or logistic reasons this intervention may not be in general use or available in the country where the study is conducted. In this situation, a trial may seek to develop an intervention that could be made available, given the finances and infrastructure of the country (for example a shorter or less complex course of treatment for a disease). The point of conducting a study in this situation may be to test an intervention that is expected or even known to be inferior to the established effective intervention, but may nonetheless be the only feasible or cost-effective and beneficial option in the circumstances. The purpose of such a study can be to make a potentially effective and affordable alternative available to the population.

However, the use of placebo control in these situations is ethically controversial for several reasons:

1. Researchers and sponsors would knowingly withhold an established effective intervention from participants in the control arm. However, when researchers and sponsors are in a position to offer an intervention to these participants and would thereby prevent or treat a serious disease, it can be difficult to see why they are under no obligation to offer this intervention. They could design the trial as an equivalency trial to determine whether the experimental intervention is as good or almost as good as the established effective intervention.

2. Some argue that it is not necessary to conduct clinical trials in populations with limited resources in order to develop interventions that are substandard compared to the available interventions in other countries. Instead, they argue that drug prices for established treatments should be negotiated and/or increased funding from international agencies should be sought.

If controversial placebo-controlled trials are undertaken then research ethics committees in the host country must:

1. seek expert opinion, if not available within the committee, as to whether use of placebo may lead to results that are responsive to the needs and priorities of the host country (see guideline 2).
2. ensure transition to care after research for study participants (see guideline 6), including post-

trial arrangements for implementing any positive trial results.

Comparative effectiveness/standard of care trials. For many conditions and diseases one or more established effective treatments exist. Physicians and hospitals may then use different treatments for the same condition. Yet often the relative merits of these treatments are unknown. Comparative effectiveness research, including systematic reviews, has received growing attention over the past years. In comparative effectiveness research, two or more recognized standards of care are being compared. Comparative effectiveness research may help to distinguish which standard of care has better outcomes or has more acceptable risks.

Although comparative effectiveness research does not typically delay or withhold an established effective intervention from participants, the risks associated with the different arms may vary substantially, for instance when surgical and medical treatment options are being compared. The risks of standard of care procedures do not necessarily qualify as minimal simply because a treatment has become standard practice. The risks to participants must be minimized and appropriately balanced in relation to the prospect of individual benefit or the social value of the research (see guideline 4).

Guideline 6: Caring for participants' health needs

Especially in the context of clinical trials, researchers and sponsors must make provisions for addressing participants' health needs during research and for the transition of participants to care when the research is concluded. The obligation to care for participants' health needs is influenced, among other things, by the extent to which participants need further assistance and by the availability of local sources of established effective care.

In situations where participants' health needs during and after research are not addressed by the local health infrastructure or the participant's pre-existing health insurance, the researcher and sponsor must make arrangements with local health authorities, members of the communities from which subjects are drawn, or non-governmental organizations such as health advocacy groups, in order to ensure that participants are adequately cared for.

Addressing participants' health needs requires at least that researchers and sponsors make plans for:

- **how care will be provided during the research when researchers discover conditions other than those under study ("ancillary care"); *and***
- **transitioning participants who continue to need care or preventive measures after the research to appropriate clinical services; *and***
- **the provision of continued access of proven beneficial study interventions; *and***
- **consultations with other relevant stakeholders, if any, to define everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has proven to be beneficial as a result of the study.**

When access is provided after research to investigational interventions that have proven beneficial, the provision may end as soon as the study intervention has been made available through the local public healthcare system or after a predetermined period of time on which the sponsors, researchers and community members agree before the start of a trial.

Information on the care for participants' health needs during and after the research must be disclosed during the informed consent process.

Commentary on guideline 6

General considerations. It is generally not appropriate to require researchers or sponsors of research to take on the role of a country's health systems. Nevertheless, research with human subjects often involves interactions that enable researchers to detect or diagnose health problems in potential participants. Similarly, the conduct of clinical research often involves the delivery of care and prevention measures in addition to testing experimental interventions. In some cases, participants may continue to need the care or prevention provided during the research after their participation in the study has ended. This may include access to an investigational intervention that has proven beneficial. At all of these points of contact, researchers and sponsors must show care and concern for the health and welfare of study participants. In part, this is justified by the principle of beneficence, which requires that researchers and sponsors act to safeguard the health of others when it is in their power to do so. But it is also supported by the principle of reciprocity; participants assist researchers in generating valuable data and, in return, researchers must ensure that participants receive care or prevention measures that they need to safeguard their health. Importantly, the obligation to care for participants' health needs is not limited to research in countries with limited resources (see guideline 2). It is a universal ethical condition for research.

Ancillary care. Sponsors are, in general, not obliged to finance interventions or to provide health-care services beyond that which is necessary for the safe and ethical conduct of research. At the same time, 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 inclusion criteria, researchers should, as appropriate, advise them to obtain, or refer them for, medical care. In some circumstances, it may be relatively easy for researchers to treat the condition themselves or refer participants to a center where treatment can be provided. In other cases, researchers may not have the expertise to treat the condition effectively and appropriate treatment may not be available locally as part of the public health system. The provision of ancillary care in this situation is a complex issue and decisions will need to be made on a case-by-case basis following discussion with research ethics committees, clinicians, researchers and representatives of government and health authorities within the host country. Thus, before research begins, agreement must be reached on how to provide care to participants in research who already have, or who develop, diseases or conditions other than those being studied. For people without access to health care, ancillary care, or participation in the research as such, may serve as an incentive to participate. Researchers and research ethics committees must prevent that this incentive becomes an undue influence to participate.

Transition to care or preventive measures after research. Because gaps in care and prevention can have significant impact on the welfare of participants, researchers and sponsors must make arrangements to transition participants to care providers after the research has ended. At a minimum, researchers must link participants who are in need of continued medical attention to an appropriate health care provider at the end of their participation in the study and communicate relevant information to this provider. Sometimes researchers themselves might continue to provide follow-up for a certain period of time, in part for research purposes, and then hand over to an appropriate provider. The obligation to transition to care after research applies to both the control group and the intervention group.

Continued access to beneficial interventions. As part of their obligation to transition to care after research, researchers and sponsors may have to provide continued access to interventions that have proven beneficial in the study or to established effective interventions that were provided as part of the standard of care or prevention provided to all participants during the course of the study. This obligation depends on a variety of factors. For example, if discontinuing an intervention will deprive

patients of basic capabilities, such as communication or functioning independently, or reduce significantly a quality of life they were able to attain during the study, then the obligation will be greater than if the intervention provides relief for a minor or transient problem. Similarly, the obligation will be greater in cases where participants are not able to access the needed care or prevention within the local health system than in cases where this is readily available. The obligation may also be greater in cases where there are no available alternatives whose clinical effectiveness is similar to the proven beneficial intervention than in cases where such alternatives exist. By contrast, the obligation may be weaker if the total number of qualifying individuals is very large (for example in the thousands).

Continued access to a beneficial study intervention can create several dilemmas:

- In the case of blinded controlled trials, it may take some time to unblind the results and to find out who has received which intervention. Researchers and sponsors must make provisions for this transition period and inform patients if they will be temporarily receiving the current standard of care before any superior intervention can be administered.
- A research ethics committee may discuss whether researchers and sponsors are under an obligation to provide participants with continued access to the experimental intervention in a non-inferiority trial. When the tested intervention is not inferior to the standard of care, there is no obligation to provide participants with the tested intervention.

The obligation to provide continued access to a study intervention that has proven beneficial in the trial may end when the intervention becomes available in the public health care system or after a predetermined period of time on which the sponsors, researchers and community members agree before the start of a trial.

Consultation with relevant stakeholders. The obligation to care for participants' health needs rests with the researcher and the sponsor. However, the delivery of such care may involve other parties, for example local health authorities, members of the communities from which participants are drawn, or non-governmental organizations such as health advocacy groups. Researchers and sponsors must describe their provisions for continued care in the study protocol and show that any other parties involved in continued care are in agreement with the plan. Research ethics committees have to evaluate whether the arrangements for continued care are adequate.

Decisions on how the transition to care obligation is met are best made for each specific study through a transparent and participatory process that involves all research stakeholders before the study begins (see guideline 7 on community engagement). This process must explore options and determine the core obligations applicable to the given situation, in terms of the level, scope, and duration of any care and treatment package post-trial, equity in eligibility to access services, and responsibility for provision and delivery. Agreements on who will finance, deliver, and monitor care and treatment must be documented.

Information to participants. Participants must be informed before the trial how the transition to care after research is arranged and to what extent they will be able to receive beneficial study interventions post-trial. Participants who receive continued access before regulatory approval must be informed about the risks of receiving unregistered interventions.

Access to study interventions for communities. Obligations to provide study interventions to communities (not continued care) are discussed in guideline 2.

See also guideline 2*: research conducted in low-resource settings* and guideline 14: *treatment and compensation for research-related harm*

Guideline 7: Community engagement

Researchers, sponsors and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, and monitoring of research, and in the distribution of its results.

Commentary on guideline 7

General considerations. A community consists not only of people living in the geographic area where research is to be carried out; it also comprises different sectors of society that have a stake in the proposed research, as well as sub-populations from which research participants will be recruited. The process must be fully collaborative and transparent, involving a wide variety of participants, including patients and consumer organizations, community leaders and representatives, relevant NGOs and advocacy groups, and community advisory boards. Proactive and sustained engagement with the communities from which subjects will be invited to participate in research is a means of showing respect for those groups and the traditions and norms that they share. The community must also participate, when feasible, in the actual discussion and preparation of the research project. Community engagement is also valuable for the contribution it can make to the successful conduct of socially valuable research. In particular, community engagement is a means of ensuring the relevance of proposed research to the affected community, as well as its acceptance by the community. In addition, active community involvement helps to ensure the ethical and scientific quality and outcome of proposed research. This is especially important when the research involves minorities or marginalized groups, including persons with stigmatizing diseases such as HIV, in order to address any potential discrimination. The research protocol must include a description of the plan for community engagement.

Community engagement might lead to pressure or undue influence on individual community members to participate (confer guideline 9 on dependent relationship). In order to avoid such pressure individual informed consent must always be sought by the researcher.

Engagement at the earliest opportunity. Before a study is initiated, the community from which participants will be recruited must be consulted about research priorities, preferred trial designs, willingness to be involved in the set up and conduct of the study. Engaging the community at the earliest stage promotes smooth study functioning and contributes to the community's capacity to understand the research process. Community members can raise any concerns they may have at the outset and as the research proceeds. Failure to engage the community can compromise the social value of the research, as well as threaten the recruitment and retention of participants. As a case in point, an HIV prevention study that had already begun was halted in Cambodia, and the same research was scheduled for Cameroon but never carried out there. In Cambodia, participants who had already been recruited protested that the informed consent process was inadequate and that no provision had been made for injuries or post-trial care and treatment. More specifically, they objected that they had not been asked whether they wanted the trial to occur in their community.

Community engagement should be an ongoing process, with an established forum for communication between researchers and community members. This can facilitate the creation of educational materials, planning the necessary logistical arrangements for the conduct of the research, and providing information about the health beliefs, cultural norms, and practices of the community. Active engagement of community members also contributes to research literacy by educating the entire community about key concepts critical for understanding the purpose and procedures of the research. Community members can assist in the development of the informed consent process and documents to ensure that they are understandable and appropriate for potential participants.

Confidence and trust. Engaging the community strengthens local ownership of the research and builds confidence in the ability of leaders to negotiate various aspects of the research such as recruitment strategies, care for the health needs of study participants, and post-trial availability of any developed interventions for populations and communities (see guidelines 2 and 6). An open and active process of community engagement is critical for building and maintaining trust among researchers, participants, and other members of the local community. An illustration of successful involvement of the community was a study in the Eliminate Dengue Program in Queensland, Australia. Previous introductions of genetically-modified strategies for dengue vector control had generated international controversy by inadequately engaging host communities. This successful episode used well-established techniques in social science to understand the community's concerns and gain their support for conducting the trial.

Roles and responsibilities. Any disagreements that may arise regarding the design or conduct of the research must be subject to negotiation between community leaders and the researchers. The process must ensure that all voices are heard, and that pressure is not exerted by community members or groups with greater power or authority. In cases of irreconcilable differences between the community and researchers, it is important to specify who should have the final say. The community may not insist on including or omitting certain procedures that could threaten the scientific validity of the research. Similarly, the research team must be sensitive to cultural norms of communities in order to support collaborative partnerships, preserve trust, and ensure relevance. The value of beginning community involvement at the earliest opportunity is that any such disagreements can be aired and if not able to be resolved, the research may have to be foregone. (See guideline 8 Collaborative Partnership).

Engagement by communities or groups. In some cases, communities or groups themselves initiate or conduct research projects. For example, patients with rare diseases may connect on online platforms and decide to collectively alter their treatment regimen while documenting the resulting clinical effects. Researchers must engage with these initiatives, which can offer valuable insights into their own work. Moreover, and to the extent possible, researchers must support experiments by patients or other individuals in order to ensure that any gathered data meet appropriate scientific standards, and that experiments are conducted in an ethically acceptable manner.

Guideline 8: Collaborative partnership and capacity building for research and review

Health-related research often requires international collaboration. Some communities lack the capacity to assess or ensure the scientific quality or ethical acceptability of health-related research proposed or carried out in their jurisdictions. Researchers and sponsors who plan to conduct research in these communities must contribute to capacity building for research and review.

Capacity-building may include, but is not limited to, the following activities:

- **strengthening research capacity**
- **strengthening research ethics review and oversight capacity in host communities (see guideline 23)**
- **developing technologies appropriate to health care and health-related research**
- **educating research and health-care personnel and making arrangements to avoid undue displacement of health care personnel**
- **engaging with the community from which research subjects will be drawn (see guideline 7)**
- **arranging for joint publication consistent with recognized authorship requirements and data sharing (see guideline 24)**

It is the responsibility of governmental authorities in charge of health-related research involving human participants to ensure that such research is reviewed ethically and scientifically by competent and independent research ethics committees and is conducted by competent research teams (Guideline 23).

Commentary on Guideline 8

General considerations. Where research capacity is lacking or underdeveloped, sponsors and researchers have an ethical obligation to contribute to a host country's sustainable capacity for health-related research and for ethical review. Before undertaking research in a community with little or no such capacities, sponsors and researchers must include in the research protocol a plan that describes the contribution they will make. The kind and amount of capacity building reasonably required must be proportional to the magnitude of the research project. A brief epidemiological study involving only review of medical records, for example, would entail relatively little, if any, such development, whereas a considerable contribution is to be expected of a sponsor of a large-scale vaccine trial intended to last several years. The conduct of research must not destabilize health care systems, and ideally should contribute to them.

Collaborative partnership. The development and testing of biomedical interventions frequently requires international cooperative research, which should transcend the disparities among countries in an ethical manner. Real or perceived disparities should be resolved in a way that ensures equality in decision-making and action. The desired relationship is one of equal partners, whose common aim is to develop a long-term collaboration through South-South and/or North-South cooperation that sustains site research capacity.

Collaborative partnership also helps to ensure the social value of research by engaging the communities in research and thereby focus on research that is considered of value to the community (see guidelines 1 and 7).

Strengthening research capacity. The specific capacity-building objectives must be determined and achieved through dialogue and negotiation between the sponsor, researchers and other relevant stakeholders, such as community boards and host-country authorities. These stakeholders must agree on joint efforts to strengthen research capacity as a component of the country's health system, Capacity may also be strengthened by studies of the incidence and prevalence of local or regional diseases, along with behavioural assessments.

Strengthening ethical review. If researchers and sponsors plan to perform research in settings where research ethics committees are absent or lack adequate training, they must help to establish such committees before the research is initiated and make provisions for their education in research ethics. To avoid conflicts of interest and safeguard the independence of review committees, financial assistance by researchers and sponsors must not be provided directly to them and must never be tied to the decision about specific protocols (confer guideline 25). Rather, funds must be made available to appropriate authorities in the host-country government or to the host research institution. In turn, governments or institutions receiving money to strengthen ethical review must not put pressure on the research ethics committee to review protocols more favorably than warranted. It is in everyone's interest to have truly independent scientific and ethical review.

Education of research personnel. Sponsors are expected to employ and, if necessary, educate individuals to function as researchers, research assistants and coordinators and data managers, for example, and to provide, as necessary, reasonable amounts of financial, educational and other assistance for capacity building.

Joint publication and data sharing. External researchers must strive to produce jointly authored, open access publications with local researchers and set up a strategy for data sharing (see guideline 24).

They must provide fair opportunities to merit joint authorship consistent with recognized authorship requirements, such as those of the International Committee of Medical Journal Editors.

(See also Guideline 2: *Research conducted in low-resource settings*)

Guideline 9: Individual informed consent

Before being enrolled in health-related research, potential participants must provide their voluntary, informed consent. Informed consent should be understood as a process. Waiving or modifying individual informed consent requires justification, and must in all cases be explicitly approved by a research ethics committee (see guideline 10).

Researchers have a duty to:

- **seek and obtain consent, but only after providing relevant information about the research and ascertaining that the potential participant has adequate understanding of the material facts; and**

- **refrain from unjustified deception or withholding of relevant information, undue influence, or coercion; and**

- **ensure that the potential participant has been given sufficient opportunity to consider whether to participate; and**

- **as a general rule, obtain from each potential participant a signed form as evidence of informed consent. Researchers must justify any exceptions to this general rule and obtain the approval of the research ethics committee.**

Researchers must renew the informed consent of each participant if there is a substantive change in the conditions or procedures of the research, or if new information becomes available that could affect the willingness of participants to continue to participate. In long-term studies, researchers must ensure at pre-determined intervals that each participant is willing to continue study participation, even if there are no changes in the design or objectives of the research.

The principal researcher has a duty that cannot be delegated to ensure that all personnel obtaining informed consent for a study comply with this guideline.

Commentary on Guideline 9

General considerations. Informed consent is a process. The start of this process requires providing relevant information to a potential participant, ensuring that the person has adequately understood the material facts and has decided or refused to participate without having been subjected to coercion, undue influence, or deception.

Informed consent is based on the principle that competent individuals have a right to choose freely whether to participate in research. Informed consent protects the individual's freedom of choice and respects the individual's autonomy.

The information must be provided in ordinary language understandable by the potential participant. The person obtaining informed consent must be knowledgeable about the research and capable of answering any questions from potential participants. Researchers in charge of the study must make themselves available to answer questions at the request of participants. Any restrictions on the participant`s opportunity to ask questions and receive answers before or during the research are unacceptable because they undermine the validity of the informed consent.

Process. Informed consent is a process that begins when initial contact is made with a potential participant and continues throughout the course of the study. Each individual must be given as much time as needed to reach a decision, including time for consultation with family members or others. Adequate time and resources must be provided for informed-consent procedures.

Content of disclosure. Appendix 2 includes the details of relevant information that must be provided, as well as possible supplementary information.

Language. Informing the individual participant must not be simply a ritual recitation of the contents of a written document. Rather, the person obtaining consent must convey the information in language appropriate for the individual's level of understanding. An oral presentation of information or the use of appropriate audiovisual aids, including pictographs and summary tables, must supplement written consent documents. The potential participant's ability to understand the information depends, among other things, on that individual's maturity, educational level and belief system. The participant's understanding also depends on the researcher's ability and willingness to communicate with patience and sensitivity, as well as the atmosphere, situation and location where the informed consent process takes place.

Comprehension. The person obtaining consent must ensure that the potential participant has adequately understood the information provided. In risky and complex studies the researcher may administer an oral or a written test to determine whether material information has been adequately understood. Researchers should use evidence-based methods for disclosure of information to ensure comprehension.

Documentation of consent. Consent may be indicated in a number of ways. The participant may express consent orally, or sign a consent form. As a general rule, the participant must sign a consent form, or, where the individual lacks decisional capacity, a legal guardian or other duly authorized representative must do so (see guidelines 16: research involving individuals who are incapable of giving informed consent and 17: children and adolescents). The research ethics committee may

approve a waiver of the requirement of a signed consent under certain conditions (see guideline 4 on modifications and waivers of informed consent). Such waivers may also be approved when existence of a signed consent form might pose a risk to the participant, for example in studies involving illegal behavior. In some cases, particularly when the information is complicated, it is advisable to give participants information sheets to retain; these may resemble consent forms in all respects except that participants are not required to sign them. Their wording must be approved by the research ethics committee. When consent has been obtained orally, researchers are responsible for providing documentation of consent to the research ethics committee.

Renewing consent. When substantive changes occur in any aspect of a study, the researcher must again seek informed consent from the participants. For example, new information may have come to light, either from the study itself or other sources, about the risks or benefits of products being tested or about alternatives to them. Participants must be given such information promptly. In most clinical trials, interim results are not disclosed to researchers or participants until the study has been concluded. In long-term studies, the willingness of each participant to continue in the study must be ensured.

Individual informed consent and access to research populations. In some circumstances a researcher may enter a community or institution to conduct research or approach potential participants for their individual consent only after obtaining permission from an institution such as school or a prison, or after permission from a community leader, a council of elders, or another designated authority. Such institutional procedures or cultural customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent. In some populations, the use of local languages may facilitate the communication of information to potential participants and the ability of a researcher to ensure that individuals truly understand the material facts. Many people in all cultures are unfamiliar with, or do not readily understand, scientific concepts such as placebo or randomization. Sponsors and researchers must develop culturally appropriate ways to communicate information necessary for adherence to the standard required in the informed consent process. Also, they must describe and justify in the research protocol the procedure they plan to use in communicating information to participants. For research conducted in multicultural settings, the project must include any resources needed to ensure that informed consent can be properly obtained in different linguistic and cultural settings.

Voluntariness and undue influence. Informed consent is voluntary if the decision to participate in research was made free from undue influence. A variety of influences may affect the voluntariness with which consent is provided. Some of these influences can be internal to participants, such as mental illness, whereas other influences can be external, such as a dependent relationship between participants and clinician-researchers. Circumstances such as severe illness or poverty may threaten voluntariness, but do not necessarily imply that participants cannot give voluntary informed consent in these situations. Research ethics committees must determine for each individual protocol if influences on voluntary consent cross the threshold of becoming undue, and which safeguards are appropriate.

Dependent relationship. There are different forms of dependent relationships, such as those between teachers and students, and guards and prisoners. In the context of clinical research dependent relationships can result from pre-existing relationships between a treating physician and a patient, who becomes a potential participant when his or her treating physician takes the role of a researcher. The dependent relationship between patients and clinician-researchers may compromise the voluntariness of informed consent, since potential participants who are patients depend for medical care upon the clinician-researcher and may be reluctant to refuse an invitation to enroll in research in which the treating clinician is involved. In some situations of dependency it is considered preferable

that the clinician provide the patient with information since she is most knowledgeable about the condition of the patient. However, to minimize the influence of the dependent relationship, several protective measures must be taken. Treating clinicians who act as researchers must acknowledge and inform patients that they have a double role of the treating clinician and researcher. They must emphasize the voluntary nature of participation and the right to withdraw. They must also assure patients that their decision whether to participate or to refuse participation will not affect the therapeutic relationship or other benefits to which they are entitled. In cases where it is necessary for the treating clinician to explain the details of the study protocol, the research ethics committee must consider whether the informed consent document must be signed in the presence of a neutral third party such as a sufficiently independent nurse or an equally qualified colleague.

Risks. Researchers must be completely objective in discussing the details of the experimental intervention, the pain and discomfort that it may entail, and known risks and possible hazards. In some types of prevention research, potential participants must receive counseling about risks of acquiring a disease and steps they can take to reduce those risks. This is especially true of research on communicable disease, such as HIV/AIDS prevention research.

Who obtains consent. Informed consent must be obtained by a member of the research team. Delegation of obtaining consent, for instance to a research nurse or another member of the research team, is allowed as long as the person who obtains consent is qualified to obtain consent and has prior experience in obtaining consent. The principal researcher is responsible for ensuring that all personnel working on the project comply with this guideline.

Length of the information leaflet. Information leaflets must be short and preferably not exceed two or three pages. The information must be clear and readable and presented using any evidence-based methods. Someone with basic education must be able to understand the leaflet. When the informed consent document is too long, there must be a short summary. In particular, information on risks that are not specific for a study, but are part of the regular treatment, must be avoided. These risks may be described in an additional leaflet with information on the standard treatment for a given condition.

Special considerations regarding informed consent for the use of data in health registries. The requirement to obtain informed consent for research on data in health-related registries may be waived, provided the conditions in guideline 10 are met. When a researcher does plan to contact persons based on their inclusion in a health-related registry, the researcher must bear in mind that these persons may be unaware that their data were submitted to the registry or unfamiliar with the process by which researchers obtain access to the data (confer guideline 12). If researchers want to contact persons included in a health registry to obtain additional information from them for new research, such studies require informed consent.

Guideline 10: Modifications and waivers of informed consent

Researchers must not initiate research involving humans without obtaining each participant's individual informed consent or that of a legally authorized representative, unless researchers have received explicit approval to do so from a research ethics committee. In such cases, before granting a waiver of consent, researchers and research ethics committees must first seek to establish whether informed consent could be modified in a way that would preserve the participant's ability to understand the general nature of the investigation and to decide whether to participate.

A research ethics committee may approve a modification or waiver of informed consent to research if

- **the research would not be feasible or practicable to carry out without the waiver or modification; *and***
- **the research has important social value; *and***
- **the research poses no more than minimal risks to participants when research interventions or procedures offer participants no potential benefits*.***

Additional provisions may apply when waivers or modifications of informed consent are approved in specific research contexts.

Commentary on guideline 10

General considerations. A modification of informed consent involves making changes to the informed consent process, most frequently in relation to the provision of relevant information and the documentation of the participant's informed consent. A waiver of consent allows researchers to conduct studies without obtaining informed consent.

As stated in Guideline 9, individuals must be given the opportunity to provide informed consent for all health-related research involving humans. Modifications or waivers of informed consent require justification and approval. In general, researchers and research ethics committees must seek to preserve as much of the informed consent process as possible. They must carefully consider whether a modification of the informed consent process would still enable participants to understand the general nature of a study and to make a meaningfully informed decision regarding whether or not to participate. For instance, in some cases it may be possible to disclose the purpose of a study without explicitly informing potential participants of the procedures in the trial arms. Waivers must be granted only in cases where a modification of the informed consent process is not possible, or would not offer participants sufficient information to make a meaningful decision about participation.

Modifying the informed consent process by withholding information in order to maintain the scientific validity of the research. It is sometimes necessary to withhold information in the consent process to ensure the validity of the research. In biomedical research, this typically involves withholding information about the purpose of specific procedures. For example, participants in clinical trials are often not told the purpose of tests performed to monitor their compliance with the regimen, since if they knew their compliance was being monitored they might modify their behaviour and hence invalidate results. In most such cases, the potential participants must be asked to consent to remain uninformed of the purpose of some procedures until the research is completed. After the conclusion of the study they have to be given the omitted information. In other cases, because a request for permission to withhold some information would jeopardize the validity of the research, participants cannot be told that some information has been withheld until the data has been collected. Any such procedure must receive the explicit approval of the research ethics committee. Moreover, before study results are analyzed, participants must receive a letter disclosing the information that was withheld and giving them the possibility to withdraw their data collected under the study.

Modifying the informed consent process by actively deceiving participants. Active deception of participants is considerably more controversial than simply withholding certain information. However, social and behavioral scientists sometimes deliberately misinform participants to study their attitudes and behavior. For example, researchers use "pseudo- patients" or "mystery clients" to study the behavior of health-care professionals in their natural settings.

Some people maintain that active deception is never permissible. Others would permit it in certain circumstances. Deception is not permissible in cases in which its use would expose participants to more than minimal risk. When deception is deemed indispensable to the methods of a study,

researchers must convince the research ethics committee that no other method could obtain valid and reliable data; that the research has significant social value; and that no information has been withheld that, if divulged, would cause a reasonable person to refuse to participate. Researchers and research ethics committees must be aware that deceiving research participants may wrong them as well as harm them; participants may resent not having been informed when they learn that they have participated in a study under false pretenses. Whenever this is necessary to maintain the scientific validity of the research, potential participants must be asked to agree to receiving incomplete information during the informed consent process (i.e., researchers obtain consent in advance for the deception). The research ethics committee must determine how deceived participants must be informed of the deception upon completion of the research. Such informing, commonly called "debriefing", ordinarily entails explaining the reasons for the deception. Debriefing is an essential part of trying to rectify the wrong of deception. Participants who disapprove of having been deceived for research purposes must be offered an opportunity to refuse to allow the researcher to use their information obtained through deception. In exceptional cases, a research ethics committee may approve the retention of non-identifiable information. For example, an option to withdraw data may not be offered in cases where research is evaluating quality of services or competence of providers (for example mystery shoppers studies).

Waiving informed consent. A research ethics committee may waive informed consent if it is convinced by the protocol that the research would not be feasible or practicable to carry out without the waiver; and the research has important social value; and the research poses no more than minimal risks to participants. These three conditions must also be met even when a study involves personally identifiable data or biological specimens, meaning that the data or specimens carry a person's name or are linked by a code to a person. The conditions must also be met when studies analyze existing data from health-related registries.

In addition, the three conditions for waiving informed consent must be met when data or biological specimens are not personally identifiable and the research has important social value. In this situation, the individuals concerned are unknown to the researcher and hence cannot be contacted to obtain informed consent. Moreover, because the data or specimens are not personally identifiable, the risks to those individuals are no greater than minimal.

Special considerations for waiving informed consent in studies performed on health-registries data. The creation and maintenance of health-related registries (for example, cancer registries, databanks of genetic and other anomalies in newborn babies) provide a major resource for many public health and epidemiological research activities relevant to issues ranging from disease prevention to resource allocation. Several considerations support the common practice of requiring that all practitioners submit relevant data to such registries: the importance of having comprehensive and accurate information about an entire population; the scientific need to include all cases in order to avoid undetectable selection bias; and the ethical principle that burdens and benefits must be distributed equitably across the population. Hence, registries that are established as mandatory by governmental authorities usually involve obligatory rather than voluntary collection of data.

When a prospective study is performed under a public health mandate or by public health authorities, such as disease surveillance, normally neither ethical review nor a waiver of consent is needed because the activity is mandated by law. Although the extent and limits of data collection are determined by law, researchers must still consider whether, in a given case, it is ethical to use their authority to access personal data for research purposes. When the use of such data does not constitute (or no longer clearly constitutes) a public health activity, the researcher must seek individual consent for the use of the data or demonstrate that the research meets the conditions for waiving informed consent, as set out in this guideline. Research projects using data from one or more

mandatory population-based registries should be submitted to a research ethics committee except for data analyses inherent to internal institutional activity of a registry.

Modified informed consent and broad informed consent. Also in biobank research individual informed consent is modified. Yet the term used for those types of consent is *broad* informed consent. The conditions for broad informed consent are discussed in guideline 11.

(See also guideline 11 on the use of stored materials)

Guideline 11: Use of stored biological materials and related data

When biological materials and related data, such as health or employment records, are stored institutions must have a mechanism to obtain authorization for future use of these materials in research.

When specimens are collected for research purposes, either specific informed consent for a particular use or broad informed consent for unspecified future use must be obtained from the source. Such broad informed consent relies on proper governance and management of the biobank. These types of consent must be obtained in the same way as described in guideline9.

When human biological materials are left over after clinical diagnosis or treatment (so-called residual tissue) and are stored for future research, a specific or broad informed consent may be used or may be substituted by an informed opt-out procedure. This means that the material is stored and used for research unless the person from whom it originates explicitly objects. The informed opt-out procedure has to fulfill the following conditions: 1) patients need to be aware of its existence; 2) sufficient information needs to be provided; 3) patients need to be told that they can withdraw their data; and 4) a genuine possibility to object has to be offered.

When researchers seek to use stored materials collected for past research, clinical or other purposes without having obtained informed consent for their future use for research, the research ethics committee may waive consent if: 1) the research would not be feasible or practicable to carry out without the waiver; *and* 2) the research has important social value; *and* 3) the research poses no more than minimal risks to participants when research interventions or procedures offer participants no potential benefits.

When researchers use coded material that is stored in a biobank the key to the code must remain with the custodian of the biobank.

Biobanks can only collect biological materials and related data from low resource settings in collaboration with local health authorities. The governance structure of such biobanks must have representation of the original setting. If the specimen and data are stored outside the original setting, there must be provisions to return all materials to the setting concerned and share possible results and benefits (see guidelines 3, 7 and 8).

Commentary on guideline 11

General considerations. The value of repositories for longitudinal studies of specific diseases is widely recognized. For this purpose, large population biobanks have been established to allow studies across many diseases through correlations of genetic, environmental, occupational, and other health data. The vast majority of people do not object to their materials—for example, bodily fluids, cells, or tissues—and related data being stored in repositories and used for research for the common good. However, the persons whose materials are stored (i.e. the donor) must explicitly authorize this undefined future use. Since it is impossible to obtain specific informed consent at the time the material is collected, because the precise nature of the research is typically unknown, an acceptable alternative to specific informed consent for future research use is broad informed consent. Such broad informed consent relies on proper governance and management of the biobank.

Governance. Institutions in which biological material and related data are archived after collection for research purposes or as “left-over” from clinical diagnosis or treatment must have a governance structure in place in which at least the following items are addressed:

- to which legal entity the material is entrusted;
- how authorization from the patient is obtained;
- how the donor can retract this authorization;

- in which circumstances donors need to be recontacted;
- a procedure for determining whether unsolicited findings should be disclosed, and if so, how they should be managed;
- how the quality of the material is controlled, ensuring the physical protection and maintenance of the materials;
- how confidentiality of the link between biological specimens and personal identifiers of the donors is maintained;
- who may have access to the materials for future research, and under which circumstances;
- which body may review research proposals for future use of the material;
- how participatory engagement with patient groups or the wider community is organized;
- to which other sources of personal information the results of analyses on biological materials may be linked;
- In broad terms which types of research will be pursued;
- which types of research will be in any case excluded or included only after recontacting the donor for consent;
- to whom the benefits, material and immaterial, from the research are expected to accrue.

Research ethics committees and biobanks. The protocol for every study using stored human biological materials and related data must be submitted to a research ethics committee, which must ensure that the proposed use of the materials falls within the scope agreed to by the donor if he or she has given specific or broad informed consent for future research. If the proposed use falls outside the authorized scope of research, re-consent is necessary. Research ethics committees may waive consent for research with historical materials provided the above three conditions mentioned in the bold text of this guideline are met (see also guideline 10 on modifications and waivers of informed consent).

Specific informed consent. When the specific use in research of the collected materials is known at the time of collection, specific informed consent must be obtained as described in guideline 9. Persons who were incompetent at the time their bodily material was stored must be given the opportunity to give informed consent or refusal when they become competent (see guideline 16).

Broad informed consent. Broad informed consent describes the range of future uses in research for which consent is given. This broad informed consent should specify: the conditions and duration of storage; who will manage access to the materials; the foreseeable uses of the materials, whether limited to an already fully defined study or extending to a number of wholly or partially undefined studies; and the intended goal of such use, whether only for research, basic or applied, or also for commercial purposes, and the possibility of unsolicited findings and how they will be dealt with. The research ethics committee must ensure that the proposed collections, the storage protocol, and the consent procedure meet these specifications.

Informed opt-out procedure for research on residual tissue. Given that human biological materials left over after clinical diagnosis or treatment (so-called residual tissue) are frequently of interest to future researchers, it is good clinical practice to offer donors several options: to have their materials used only for their own treatment or benefit and then discarded; to allow stored materials to be used for a specifically described research project (specific informed consent); or to allow stored materials to be used for yet undefined research, with or without personal identifiers. However, this practice can be difficult to implement, and, an informed opt-out procedure may therefore be acceptable. This implies the material is stored and used for research unless the person from whom it originates explicitly objects.

The informed opt-out procedure has to fulfill the following conditions: 1) patients need to be aware of its existence; 2) sufficient information needs to be provided; and 3) patients need to be informed that they can withdraw their data; and 4) a genuine possibility to object has to be offered.

An informed opt-out procedure for research on residual tissue may not be appropriate in certain circumstances, namely a) when it involves more than minimal risks to the patient, or b) when controversial or high impact techniques are used, for example the creation of immortal cell lines, or c) when research is conducted on sensitive tissue types, for example gametes, or d) when research is conducted in contexts of heightened vulnerability, for example certain psychiatric patients. A research ethics committee must determine whether explicit informed consent for the research is required.

Authorization for research with archived materials. When existing repositories of biological materials and data collected and stored in the past without explicit informed consent offer important and otherwise unobtainable data, a research ethics committee needs to decide whether the use of such materials is justified in the absence of explicit consent. The most common justification for using records or materials collected in the past without consent is that it would be impracticable or prohibitively expensive to locate the persons whose materials or records are to be examined; this may happen when, for instance, the study involves reviewing hospital records or performing new tests on blood materials collected at a time when consent to future research uses of such materials was not usually sought. In addition the research must have important social value; and the research must pose no more than minimal risks to participants when research interventions or procedures offer participants no potential benefits.

Anonymization or coding. Biological material that is stored in biobanks must be anonymised or coded. When researchers use coded materials from biobanks in later studies, the key to the code must remain with the custodian of the biobank. Thus researchers can only use anonymized or coded material.

Return of results and disclosure of (un)solicited findings. Especially in the context of repositories established for longitudinal study of a particular disease, the informed consent must clearly stipulate what return of information–if any–derived from analysis of the materials is foreseen, should the participant so wish. There is an emerging consensus that at least some subsets of (genetic) research findings must be returned to individual donors if they wish so.

Any disclosure policy of (un)solicited findings must be designed and discussed with the community of donors beforehand. Tiered consent, i.e. working with packages or ‘tiers’ of information, gives donors a range of choices and allows them to choose some options over others to give them greater control over the use of their biological materials. In general, life-saving information and data of immediate clinical utility involving a significant health problem must be offered for disclosure, whereas information of uncertain scientific validity or meaning would not qualify for communication to the participant.

Children and adolescents and biobanks. Children and adolescents who reach the age of maturity must be given the opportunity to give broad informed consent to continue the storage and use of their collected material and data, and they must at this point also be able to withdraw their consent for future research. An informed opt-out system in which persons are explicitly approached and alerted to their right to withdraw, could also be acceptable.

Storing and using material from low-resource settings in biobanks. Biobanks have become a global phenomenon. At the same time, there may be less experience with storing and using biological material in some low-resource settings. In addition to what is stated in this guideline, requirements for

community engagement, capacity building and equitable distribution of burdens and benefits of research as described in other guidelines also apply to biobank research in low-resource settings (see guidelines 3,7,8).

Guideline 12: Use of health-related data in research

When health-related data are stored, institutions must have a mechanism to obtain authorization for future use of these data in research.

If data are collected for research purposes either informed consent for a specific use or broad informed consent for unspecified future use must be obtained from the source. These types of informed consent must be obtained in the same way as described in guideline 3.

When data are used that were collected in the context of routine clinical care, an informed opt-out procedure must be used. This means that the data may be stored and used for research unless a person explicitly objects to this use, such objection being not applicable to data subject to mandatory inclusion in population-based registries. The informed opt-out procedure has to fulfill the following conditions: 1) patients need to be aware of its existence; 2) sufficient information needs to be provided; 3) patients need to be informed that they can withdraw their data; and 4) a genuine possibility to object has to be offered.

When researchers seek to use stored data collected for past research, clinical or other purposes without informed consent to their use for research, the research ethics committee may consider waiving the consent of individuals consent if: 1) the research would not be feasible or practicable to carry out without the waiver; *and* 2) the research has important social value; *and* 3) the research poses no more than minimal risks to participants when research interventions or procedures offer participants no potential benefits.

When researchers use coded health-related data, the key to the code must remain with the custodian of the biobank.

Researchers are only allowed to use anonymized or coded health-related data. The key to the code must remain with the custodian of the databank.

Databanks can only collect data from low resource settings in collaboration with local health authorities. The governance structure of such a databank must have representation of the original setting. If the collection is stored outside the original setting there must be provisions to return all data to the setting concerned and share possible results and benefits.

Commentary on guideline 12

General considerations. The value of data collections for longitudinal studies of specific diseases is widely recognized. Like with biobanks, a vast majority of people do not object to their data being stored in collections and used for research for the common good. Such collections share an important characteristic: the persons whose data are stored explicitly agree to this future not yet defined use. Therefore it will be impossible to obtain specific informed consent at the time of the collection of the data. An acceptable alternative is broad informed consent. Broad informed consent relies on proper governance.

Governance. Institutions where data are collected and archived must have a governance structure in place in which at least the following items are regulated:

- to which legal entity the material is entrusted;
- how authorization from the donor is obtained;
- how the donor can retract this authorization;
- in which circumstances donors need to be recontacted;
- a procedure for determining whether unsolicited findings should be disclosed, and if so, how they should be managed;
- how the quality of the collection is controlled;
- how confidentiality of the link between collected data and personal identifiers of the donors is maintained;
- who may have access to the data for future research, and under which circumstances;
- which body may review research proposals for future use of the data;
- how participatory engagement with patient groups or the wider community is organized;

- to which other sources of personal information the results of analyses with data may be linked;

- In broad terms which types of research will be pursued;
- which types of research will be in any case excluded or included only after recontacting the donor for consent;
- to whom the benefits, material and immaterial, from the research are expected to accrue.

Research ethics committees and storing health-related data. The protocol for every study using collected data must be submitted to a research ethics committee, which must ensure that the proposed use of the data falls within the scope specifically agreed to by the participant. If not, re-consent is necessary.

Data mining. Some entities collect data that may be "mined" for health-related research, even if they are not collecting health-related data deliberately (for example queries in search engines, consumer choices on websites). Such entities must strive for governance structures and mechanisms to obtain authorization for future use of these data in research as discussed in this guideline.

Confidentiality. An important aspect of storing health-related data is the confidentiality between researcher and patient. The collection and storage of information could, if disclosed to third parties, cause harm, stigma or distress. Researchers must arrange to protect the confidentiality of such information by, for example, by using anonymized or coded data and limiting access to the information of third parties. During the process of obtaining informed consent, the researcher must inform the potential patients about the safeguards that will be taken to protect confidentiality as well as their limitations.

When linked data and materials are used, researchers customarily discard personal identifying information when consolidating data for purposes of statistical analysis; this also occurs when researchers have linked (or coded) different sets of data regarding individuals with the consent of individual participants. When project plans require personal identifiers to remain on records used for a study, researchers must explain to research ethics committees why this is necessary and how confidentiality will be protected. It can be acceptable to store personally identifiable data to enhance their value for future research; by implication, efforts to de-identify data in order to safeguard confidentiality and the resulting trade-offs in the scientific value of the given data need to be carefully balanced.

Limits of confidentiality. Potential participants must be informed of limits to the ability of researchers to ensure strict confidentiality and of the potential adverse consequences of breaches of confidentiality. Confidentiality is limited for three reasons. First, even with good governance structures, there is some background risk that data are leaked or stolen and thus are obtained by unauthorized third parties. Second, data from different sources (for example, health records, employment records, etc.) may be linked due to technological advances, which increasingly enables researchers or others to identify individuals even when working with anonymized or coded data. Identification is also possible when the context in which the research is conducted is narrow (for example small hospital) or very specific (for example patients with rare diseases). Pooling data from a number of comparable sources may reduce but not completely eliminate the possibility of identifying individuals. In addition, genetic information derived through comprehensive technologies (for example whole-genome sequencing) increasingly allows identifying individuals. Third, releasing confidential data can be required by law. For example, some jurisdictions require the reporting to appropriate agencies of certain communicable diseases or evidence of child abuse or neglect. Similarly, (health) authorities and research ethics committee accrediting agencies may have the legal right to inspect study records, and a sponsor's compliance audit staff may require and obtain access to confidential data. These and similar limits to the ability to maintain confidentiality must be anticipated and disclosed to potential participants (see guideline 9, individual informed consent).

Mandatory population-based registries. Research projects using data from mandatory population-based registries must be submitted for review to a research ethics committee except for data analyses inherent to the internal institutional research activity of the registry.

Specific informed consent When the specific use in research of the collected data is known at the time of collection, specific informed consent must be obtained as described in guideline 9. Persons who were incompetent at the time their data was stored must be given the opportunity to give informed consent or refusal when they become competent (see guideline 16).

Broad informed consent. Broad informed consent describes the range of future uses in research for which consent is given. This broad informed consent should specify: the conditions and duration of storage; who will manage access to the data; the foreseeable uses of the data, whether limited to an already fully defined study or extending to a number of wholly or partially undefined studies; and the intended goal of such use, whether only for research, basic or applied, or also for commercial purposes, and, if applicable, the possibility of unsolicited findings and how they will be dealt with. The research ethics committee must ensure that the proposed collections, the storage protocol, and the consent procedure meet these specifications.

Secondary use of stored data. Sometimes data are collected in databanks, during research or during other activities (for example clinical practice, health insurance), that can be used in future research. Typically the precise research questions will be unknown at the time of data collection. In those cases it is acceptable to use the data for secondary analysis when the intended use falls within the scope of the original broad informed consent.

Archived data When existing data, collected and stored without an explicit consent process, offer important and otherwise unobtainable information, a research ethics committee needs to decide whether the use of such data is justified in the absence of explicit consent. The most common justification for using data collected in the past without consent is that it would be impracticable or prohibitively expensive to locate the persons whose data are to be examined. This may happen when, for instance, the study involves reviewing hospital records from a time when consent to future research uses of such data was not usually sought. However, data from individuals who have specifically rejected such uses in the past may be used only with proper, official authorization in public health emergencies.

Informed opt-out procedure for research with health-related data. In the absence of broad informed consent, an informed opt-out consent procedure can be used. This means that the data is stored and used for research unless a person explicitly objects. The informed opt-out procedure has to fulfill the following conditions: 1) people need to be aware of its existence; 2) sufficient information needs to be provided; 3) a genuine possibility to object has to be offered. However, in certain circumstances the researcher must obtain explicit informed consent, whether specific or broad: 1) when the research involves higher risks are involved; or 2) when controversial or high impact techniques are used; or 3) when the research is conducted with certain vulnerable patients, for example psychiatric patients. A research ethics committee must determine whether explicit informed consent is required.

Re-contacting participants. Long term projects often include plans to search for and re-contact participants who have been lost to follow-up. Such outreach might also occur when researchers want to obtain consent for a new use of stored biological material or data that still has personal identifiers. Participants or service users must be made aware of this possibility at the time of initial consent and given the choice to opt-out of being re-contacted. Researchers must also establish acceptable modalities for establishing contact with those participants or service users who are willing to be reached out to for the above-mentioned purposes.

In cases where a researcher does plan to contact persons based on their inclusion in a health-related registry, the researcher must bear in mind that these persons may be unaware that their data were submitted to the registry or unfamiliar with the process by which researchers obtain access to the data. If researchers want to contact persons included in a health registry to obtain additional information from them for new research, such studies require individual informed consent (see guideline 9).

Return of results and (un)solicited findings. Especially in the context of data collections in which large data bases are combined (big data research), the informed consent must clearly stipulate what return of information–if any–derived from analysis of the data is foreseen, should the subject so wish. Tiered consent--working with packages or 'tiers' of information, gives donors a set of choices and allows them to choose some options over others to give them greater control of the use of their data. In general, life-saving information and data of immediate clinical utility that entail a significant health problem must be offered for disclosure, whereas information of uncertain scientific validity or meaning would not qualify for communication to the donor.

Data-sharing. Researchers, sponsors and research ethics committees must share data for further research where possible. The conditions for data-sharing are spelled out in guideline 24.

Children and adolescents and collected data. Children and adolescents who reach the age of maturity must be given the opportunity to give broad informed consent to continue the storage and use of their collected data and must then also be able to withdraw. An informed opt-out system in which persons are explicitly approached and alerted to their right to withdraw, could also be acceptable.

Storing and using data from low-resource settings in biobanks. Databanks have become a global phenomenon. At the same time, there may be less experience with storing and using data in some low-resource settings. In addition to what is stated in this guideline, requirements for community engagement, capacity building and equitable distribution of burdens and benefits of research as described in other guidelines also apply to databank research in low-resource settings (see guidelines 3,7,8).

Guideline 13: Reimbursement and compensation for research participants

Research participants must be reasonably reimbursed for direct and indirect expenses incurred during the research, such as travel costs and lost earnings, and compensated reasonably for inconvenience and time spent. Compensation can be monetary or non-monetary. The latter might include free health services unrelated to the research, medical insurance, educational materials, or other benefits.

Compensation must not be so large as to induce potential participants to consent to participate in the research against their better judgment ("undue inducement"). A local research ethics committee must approve reimbursement and compensation for research participants.

Concerns about undue inducement must not preclude the study of monetary or material incentives as a potential way of promoting healthy behaviors.

Commentary on Guideline 13

General considerations. Participants should not have to pay for making a contribution to the social good of research, whether in the form of direct expenses (for example transportation costs) or indirect expenses (for example lost earnings), and must therefore be reasonably reimbursed for such expenses. In addition, participants must be appropriately compensated for the time spent and other inconveniences resulting from study participation. The obligation to reasonably reimburse and compensate participants arises even when study enrollment offers participants potential benefits (for example investigational drug). This because the vast majority of clinical research studies involve research procedures that have no potential benefits for participants but are performed for research purposes, such as additional blood draws, extra hospital visits, and overnight stays. Moreover, it cannot be known before the research that investigational interventions will benefit participants. Indeed, some investigational interventions will prove to cause more harm than good.

Appropriate compensation. Participants must also be reasonably compensated for their inconvenience and time spent participating in research. Compensation can be monetary or non-monetary and may include, for example, health services unrelated to the research, medical insurance, educational materials, counseling, or food supplies. Especially when the research poses low risks, providing compensation for participating usually does not raise concerns about undue inducement.

Unacceptable compensation. Monetary or in kind compensation for research participants must not be so large as to persuade them to volunteer against their better judgment or deeply held beliefs ("undue inducement"). It can be difficult to evaluate whether an undue inducement exists, in part because the compensation that makes someone volunteer against their better judgment depends on their personal situation. An unemployed person or a student may view compensation differently from an employed person.

Research ethics committees must evaluate monetary and other forms of compensation in light of the traditions and socio-economic context of the particular culture and population in which they are offered, in order to determine whether the average participant expected to enroll in the study is likely to participate in the research against their better judgment because of the compensation offered. Consultation with the local community may help to ascertain this. Especially as the risks of research procedures that have no potential benefits for participants increase, so does the concern that compensation may constitute an undue inducement.

Compensation for incompetent persons. Incompetent persons may be vulnerable to exploitation for financial gain by their guardians. A guardian asked to give permission on behalf of an incompetent person must be offered no compensation other than reimbursement for travel and other direct or indirect expenses. Where it would be reasonable to provide compensation to the participants themselves, their lack of decisional capacity must not preclude researchers from doing so. When participants are incompetent, compensation must be given in a way that participants themselves can benefit from it, not the guardians.

Compensation after study withdrawal. When a researcher withdraws a participant from a study on health-related grounds, the person must be compensated as if full study participation had taken place. If the withdrawal is due to a research-related harm, this harm must be treated and the participant is entitled to additional compensation as set out in guideline 14. When researchers must withdraw a participant from the study for willful noncompliance, they are entitled to withhold part or all of the payment. Participants who do not continue study participation for other reasons must be compensated

in proportion to the amount of participation they completed. Researchers must not withhold *all* of the monetary compensation until the end of studies involving more than one session or intervention in order to induce unwilling participants to remain in the study. The conditions for compensation must be approved by the research ethics committee and disclosed during the informed consent process.

Studies of financial incentives. In some studies, monetary or material incentives to participants are themselves a core object of study, rather than a form of compensation. For example, incentives in the form of cash transfers or vouchers might be tested as a means of overcoming economic obstacles to treatment (for example to accessing healthcare and continuing treatment) or a lack of effective motivation for treatment (for example in long-term treatment for some chronic conditions). Concerns about undue inducement must not preclude the conduct of such research, but research ethics committees must be sensitive to risks that might emerge for research using incentives.

See also guideline 9: *individual informed consent* and guideline 25: *conflicts of interest*.

Guideline 14: Treatment and compensation for research-related harms

Sponsors and researchers must **ensure that research participants who suffer physical, psychological or social harm as a result of participating in health-related research receive free treatment and rehabilitation for such harms, as well as compensation for lost wages, as appropriate. Such treatment and compensation is owed to research participants who are harmed, physically, psychologically or socially, as a consequence of interventions performed solely to accomplish the purposes of research, regardless of fault. In the case of death as a result of research participation, the participant's dependents are entitled to compensation. Participants must not be asked to waive the right to free treatment and compensation for research-related harms.**

Research ethics committees must evaluate whether there is an adequate arrangement for treatment and compensation for injuries.

Commentary on Guideline 14

General considerations. This guideline focuses on the entitlement to free treatment and additional compensation when research participants are harmed by research interventions or procedures. In the commentary below the thresholds for such entitlements are described. In that context there is also an entitlement of dependents to material compensation for death or disability occurring as a direct result of study participation. Not having a proper mechanism in place for compensation of research harms may serve as a disincentive for people to participate in research, and may negatively impact trust in the research enterprise. Therefore it is not only just, but also pragmatic to have appropriate provision for free treatment and compensation for research-related harms.

Obligation of the sponsor with regard to free treatment and rehabilitation. Sponsors and researchers must ensure that research participants who suffer physical, psychological or social harm as a result of participating in health-related research receive free treatment and rehabilitation for such harms. This

will usually mean that in one way or another continuity of care for participants' health needs is guaranteed without any cost to the participant for as long as such care is needed (confer Guideline 6). This treatment or rehabilitation must be provided for free, since the harm resulted from the research.

Obligation of the sponsor with regard to compensation. Before the research begins, the sponsor, whether a pharmaceutical company, other organization or institution, or a government (where government insurance is not precluded by law), must agree to provide compensation for any harm for which participants are entitled to compensation based on this guideline, or come to an agreement with the researcher concerning the circumstances in which the researcher must rely on his or her own insurance coverage (for example, for negligence or failure of the researcher to follow the protocol, or where government insurance coverage is limited to negligence). In certain circumstances it may be advisable to follow both courses. Sponsors must seek adequate insurance against risks to cover compensation, independent of proof of fault.

Equitable compensation and free medical treatment. Compensation is owed to research participants who are harmed, psychologically, physically or socially, as a consequence of interventions performed solely to accomplish the purposes of research. A harm can be considered a consequence of the intervention when the harm would not have happened but for the person's participation in research and is different in kind or magnitude from the sorts of harms that would have been reasonable for that participant to expect had he or she just received clinical care (for participants who are also patients, rather than healthy participants). Compensation must be equitable: researchers and sponsors do not have an obligation to pay for care for *any* harm that befalls a participant while in a study. The amount of compensation must also be based on pre-specified models of calculation, which must be made available by regulatory bodies and is usually based on national jurisprudence. The research ethics committee must be satisfied that there is an adequate arrangement for treatment and compensation for research-related harms and provide oversight that researchers report on such harms, how treatment is being paid for and compensation is provided to participants, and what is being offered.

Participants must not be asked to waive their rights to free treatment or compensation for research-related harms, nor must they be required to show negligence or lack of a reasonable degree of skill on the part of the researcher in order to claim free treatment or compensation. The informed consent process or form must contain no words that would absolve an researcher from responsibility in the case of harm, or that would imply that participants would waive their right to seek compensation (see guideline 9). Prospective participants must be informed that they will not need to take legal action to secure the free treatment or compensation for harm to which they may be entitled. They must also be told what medical service or organization or individual will provide the treatment and what organization will be responsible for providing compensation.

Guideline 15: Research involving vulnerable persons

When vulnerable individuals and groups are considered for recruitment in research, researchers and research ethics committees must ensure that specific protections are in place

to safeguard the rights and welfare of these individuals and groups in the conduct of the research.

Commentary on Guideline 15

General considerations. According to the *Declaration of Helsinki*, vulnerable groups and individuals "may have an increased likelihood of being wronged or of incurring additional harm." In some cases, persons are vulnerable because they are relatively (or absolutely) incapable of protecting their own interests. This may occur when persons have relative or absolute impairments in decisional capacity, education, resources, strength, or other attributes needed to protect their own interests. In other cases, persons can also be vulnerable because some feature of the circumstances (temporary or permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their interests. This may happen when people are marginalized, stigmatized, or face social exclusion or prejudice that increases the likelihood that others place their interests at risk, whether intentionally or unintentionally. Although research ethics committees can require special protections only for groups considered for enrolment in a particular project, researchers and others involved in research must take into account factors that render individual potential or enrolled participants vulnerable and take appropriate steps to mitigate those factors.

A traditional approach to vulnerability in research has been to label entire classes of individuals as vulnerable. The account of vulnerability in this guideline seeks to avoid considering entire classes of individuals as vulnerable. However, it is useful to look at the specific characteristics that may render individuals vulnerable, as it can aid in identifying the special protections needed for persons who may have an increased likelihood of being wronged or of incurring additional harm as participants in research.

Some characteristics can make it reasonable to assume that certain populations are vulnerable, for example:

Capacity to consent. One widely accepted criterion of vulnerability is limited capacity to consent or decline to consent to research participation. Individuals with this characteristic are discussed in other guidelines in this document (Guidelines 16: persons who are incapable of giving informed consent and 17: Children and adolescents)

Individuals in hierarchical relationships. The characteristic of vulnerability in this case is the possibility of diminished voluntariness of the consent of potential participants who are in a subordinate relationship. Examples are medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police. Their agreement to volunteer may be unduly influenced, whether justified or not, by the expectation of preferential treatment if they agree to participate in the study or by fear of disapproval or retaliation if they refuse (see also commentary to guideline 9). The research protocol must include a description of provisions to protect such individuals from being conscripted into research.

Institutionalized persons. Residents of nursing homes, mental institutions, and prisons are often considered vulnerable because in a confined setting they have few options and are denied certain freedoms that non-institutionalized persons enjoy. For example, prisons have been described as "an inherently coercive environment." Also they may be in a dependent relationship with caregivers or guardians (see dependent relationship guideline 9).

One protection for institutionalized individuals is the appointment of an advocate of some sort to the research ethics committee when such proposals are under review (confer the dependent relationship in guideline 9). Some individuals with this characteristic may also have diminished capacity to

consent, and therefore require the additional protections noted earlier for participants who lack decisional capacity.

Women. Although in general women must not be considered vulnerable, specific circumstances in which women may be considered vulnerable in research include: research on intimate partner violence; studies of abortion in jurisdictions where abortion is illegal; research with women who live in a cultural context where they are not permitted to consent on their own behalf for participation in research, but require permission from a spouse or male relative. When women in such situations are potential participants in research, researchers need to exercise special care (see guideline 18).

Pregnant women. Pregnant women must not be considered vulnerable simply because they are pregnant. Specific circumstances, such as risks to the fetus, may require special protections, as set out in guideline 19.

Other potentially vulnerable individuals. Among members of groups that have traditionally been considered vulnerable, the following are frequently mentioned: people receiving welfare benefits or social assistance and other poor people and the unemployed; people who perceive participation as the only means of accessing medical care; some ethnic and racial minorities; homeless persons, nomads, refugees or displaced persons; people living with disabilities; patients with incurable disease; individuals who are politically powerless; and members of communities unfamiliar with modern medical concepts.

To the extent that these and other people have one or more of the characteristics discussed above, research ethics committees must review the need for special protection of their rights and welfare, and include such protections when necessary. However, researchers and research ethics committees must avoid making judgments regarding the exclusion of such groups based on stereotypes. One proposed mechanism that can be used to avoid stereotyping is community consultation, where feasible, before and during the conduct of the research (see guideline 7 on community engagement).

Special protections. Special protections for these groups can include allowing no more than minimal risks for procedures that offer no potential benefits for participants; supplementing the participant's agreement by the permission of family members, legal guardians, or other appropriate representatives; or requiring that the research be carried out only when it is targeted at conditions that affect these groups. Research ethics committees need to be sensitive to not overly excluding people, and allow them to participate by specifying special protections.

Guideline 16: Research involving individuals who are not capable of giving informed consent

Individuals who are not capable of giving informed consent may have distinctive health needs that require research in this population. At the same time, they may not be able to protect their own interests due to their lack of capacity to provide informed consent. Specific protections to safeguard the rights and welfare of these subjects in research are therefore necessary.

Before undertaking research with individuals who are incapable of giving informed consent, the researcher and the research ethics committee must ensure that

- **a legally authorized representative of the person who is incapable of giving informed consent has given permission and this permission takes account of the participant's previously formed preferences and values; *and***

- **the assent of each subject has been obtained to the extent of that person's capacity, after having been provided with adequate information about the research at the level of the subject's capacity for understanding this information; *and***

- **in the case of emergency research, participants have made advance directives, where feasible, for participation in research while fully capable of giving informed consent or their communities have been engaged.**

For research interventions or procedures that have the potential to benefit individuals who are incapable of giving informed consent, the risks must be minimized and outweighed by the prospect of individual benefit.

If participants become capable of giving informed consent during the research, their consent to continued participation must be obtained.

In general, a potential participant's refusal to enroll in the research must be respected, unless, in exceptional circumstances, research participation is considered the best available medical alternative for the individual who is incapable of giving informed consent.

For research interventions or procedures that have no potential benefits for participants, two conditions apply:

- **the risks must be minimized and no more than minimal, *and***

- **they must be studied first in persons who can give consent when these interventions and procedures are targeted at conditions that affect persons who are not capable of giving informed consent as well as those who are, unless the necessary data cannot be gathered without participation of persons who are incapable of giving informed consent.**

When the social value of the studies with such research interventions and procedures is compelling, and these studies cannot be conducted in persons who can give informed consent, a research ethics committee may permit a minor increase above minimal risk.

Commentary on Guideline 16

General considerations. In general, competence or decisional capacity is determined by the ability to understand material information, appreciate the situation and its consequences, reason about the treatment options, and communicate a choice. Participants may be incapable to give informed consent for a variety of reasons (for example dementia, some psychiatric conditions and accidents). Moreover, lack of capacity is time, task and context specific. Persons can become capable of giving informed consent after a certain period, or they can be incompetent to decide whether they should be treated for a certain disease but competent to decide whether they want to enjoy a meal. In order to adequately treat people who suffer from conditions related to their decisional capacity, research with incapacitated participants is essential.

When researchers have reason to believe that potential or current participants are incapacitated, the participant's decisional capacity must be adequately assessed. In cases where incompetence might reasonably be expected, participants must be routinely screened. However, it is important to note that diagnosis of a mental or behavioral disorder does not necessarily imply that individuals are incapable of giving informed consent.

Minor increase above minimal risk. Research risks are minimal when the risk of serious harm is very unlikely and the potential harms associated with more common adverse events are low (see guideline 4). Risks in research must be compared to risks that an average, normal, healthy individual experiences in daily life or during routine examinations. If the risks are considered as minimal in these situations, they may also be considered as minimal in clinical research (see guideline 4). A research ethics committee may permit a minor increase above minimal risk for research interventions and procedures that have no potential benefits when the necessary data cannot be gathered in incapacitated persons and in a less risky or burdensome manner, and the social value of the research is compelling. While there is no precise definition of a "minor increase" above minimal risk, the increment in risk must only be a fraction above the minimal risk threshold and considered acceptable by a reasonable person.

Assent and dissent. If participants cannot consent because they are incapacitated due to mental or behavioral disorders, they must be engaged in the research discussion at the level of their capacity to understand, and they must be given a fair opportunity to agree to or to decline participation in the study. This can also be called obtaining the participant's assent or dissent. Assent and dissent must be considered as a process that responds to changes in the person's cognitive status (see guideline 9).

Absence of affirmative agreement or explicit objection must be respected unless the treating physician and representative regard participation in research as the best available medical alternative. Any explicit objection by persons who are incapable to give informed consent due to mental or behavioral disorders must be respected even if the legally authorized representative has given permission. An explicit objection may be overruled if the incapacitated person with the mental or behavioral disorder needs treatment that is not available outside the context of research, the research intervention shows a clear prospect of clinical benefit (confer guideline 4), and the treating physician and the legally authorized representative consider the research intervention to be the best available medical alternative for the person lacking capacity.

Permission of a legally authorized representative. In accordance with national regulation, the permission of an immediate family member or other person with a close personal relationship with the individual must be sought. Surrogate decision makers must evaluate to what extent study participation is consistent with the individual's preferences and values, and – in the case of research that offers participants a prospect of clinical benefit – to what extent study participation promotes the individual's clinical interests. Previously stated or documented preferences regarding the individual's willingness to enroll in research must be respected. Researchers must recognize that surrogates may have their own interests that may call their permission into question.

Emergency care situations in which the researcher anticipates that many participants will be unable to consent. Research protocols are sometimes designed to address conditions occurring suddenly and rendering the patients or participants incapable of giving informed consent. Examples are sepsis, head trauma, cardiopulmonary arrest and stroke. In such circumstances it is often necessary to proceed with the research interventions very soon after the onset of the condition in order to evaluate an investigational treatment or develop the desired knowledge.

If possible, an attempt must be made to identify a population that is likely to develop the condition to be studied. This can be done readily, for example, if the condition is one that recurs periodically in individuals, such as grand mal seizures and alcohol binges. In such cases, researchers should ideally contact potential participants while fully capable of informed consent, and obtain their agreement to be involved in the research during future periods of incapacitation.

If there is no opportunity to solicit informed consent of participants while fully capable of informed consent, plans to conduct emergency care research with incapacitated persons must be publicized within the community in which it will be carried out, where feasible. In the design and conduct of the research, the research ethics committee, the researchers and the sponsors must be responsive to the concerns of the community. If there is cause for concern about the acceptability of the research in the community, there must be a formal consultation with representatives designated by the community. The research must not be carried out if it does not have substantial support in the community concerned. (See guideline 4 commentary, *Risks to groups of persons*, and guideline 7 on Community engagement)

Before proceeding without prior informed consent, the researcher must make reasonable efforts to locate a legally authorized representative to give permission on behalf of an incapacitated patient in need of emergency care. If such a person can be located and refuses to give permission, the patient may not be enrolled as a participant**.** The risks of all interventions and procedures will be justified as required by guideline 4.The researcher and the research ethics committee must agree to a maximum time of involvement of an individual without obtaining either the individual's own informed consent or surrogate consent according to national regulation if the person continues to be unable to give consent. If by that time there is no individual or surrogate consent, the participant must be withdrawn from the study provided that withdrawal will not make the participant worse off. The participant or the surrogate must be offered an opportunity to object to the use of data derived from participation of the patient without consent or permission.

When there are no advance directives for research participation for the period of incapacitation, permission of a legally authorized representative must be sought. This permission must take account of the participant's previously formed preferences and values.

In all cases in which research has been approved to begin without prior consent of incapacitated persons because of suddenly occurring conditions, they must be given all relevant information as soon as they regain capacity, and their consent to remain in the study must be obtained as soon as is reasonably possible. In addition, they must be given the opportunity to opt out from the study.

Guideline 17: Research involving children and adolescents

Children and adolescents have distinctive physiologies and health needs that require research in this population. Research designed to obtain knowledge relevant to the health needs of children and adolescents must therefore be promoted. However, their distinctive physiologies may also place children and adolescents at increased risk of being harmed in the conduct of research. Moreover, they may not be able to protect their own interests due their developing capacity to give informed consent. Specific protections to safeguard children's rights and welfare in the research are therefore necessary.

Before undertaking research involving children and adolescents, the researcher and the research ethics committee must ensure that

- **a parent or a legally authorized representative of the child or adolescent has given permission.**

- **the agreement (assent) of the child or adolescent has been obtained in keeping with the child's/adolescent's capacity after having been provided with adequate information about the research tailored to the child's/adolescent's maturity.**

If children reach the legal age of maturity during the research, their consent to continued participation must be obtained.

In general, the refusal of a child or adolescent to participate or continue in the research must be respected, unless, in exceptional circumstances, research participation is considered the best medical alternative for the child.

For research interventions or procedures that have the potential to benefit children or adolescents, the risks must be minimized and outweighed by the prospect of individual benefit.

For research interventions or procedures that have no potential benefits for participants, two conditions apply:

- **the risks must be minimized and no more than minimal, *and***

- **they must be studied in adults first,when these interventions and procedures are targeted at conditions that affect adults as well as children and adolescents, unless the necessary data cannot be gathered without participation of children or adolescents.**

When the social value of the studies with such research interventions and procedures is compelling, and these studies cannot be conducted in adults, a research ethics committee may permit a minor increase above minimal risk.

Commentary on Guideline 17

Justification of the involvement of children and adolescents in health-related research. The participation of children and adolescents is indispensable for research into diseases of childhood and conditions to which they are particularly susceptible, as well as for clinical trials of drugs that will be used for children and adolescents as well as adults. In the past, many new products were not tested in children or adolescents though they were directed towards diseases also occurring in childhood. In some cases this resulted in children being exposed to interventions that were not effective or that were harmful. In general, this lack of information results in higher risks for children and adolescents from being exposed to interventions where little is known about their specific effects or safety in this population. Therefore, it is imperative to involve children and adolescents in research to study both investigational interventions for childhood conditions and established interventions in adults that are also relevant for children or adolescents, but that have not previously undergone rigorous testing in children and adolescents.

Order of involvement in research. There is a controversy over whether research must be done first in adults or adolescents before it is done in (younger) children. Some think that all studies must be done in adults first in order to minimize risks in children. Others argue that this requirement can preclude valuable and timely research in children, in particular when the research addresses an important health need or priority of children.

These guidelines acknowledge the general rationale behind inclusion of adults before children is that children must be protected from unnecessary risks of harm. However, a strict adherence to this requirement may not always be tenable in pediatric research since children and adolescents face distinctive health problems. In the case of childhood specific conditions, studies in adults would not be feasible nor their results meaningful. Moreover, in rare cases (for example when a disease affects large numbers of people, including children and adolescents, the available treatment options are limited, and an investigational agent shows great promise), waiting for conclusive results from research in adults before initiating pediatric studies can significantly delay the development of beneficial interventions.

The current guidelines do not require that research first be conducted in adults if the research includes interventions that hold out the prospect for individual benefit for participants. This prospect is sufficient to justify the risks associated with the interventions and procedures, provided the cumulative risk of all study interventions and procedures that do not hold out the prospect of individual benefit is no more than minimal. If research meets these conditions but the cumulative risk of all study interventions and procedures that do not hold out the prospect of individual benefit is only a minor increment above

minimal risk, then research ethics committees must be convinced that the research is of special relevance to children or adolescents and could not be carried out equally well in an adult population. In such cases, older children who are more capable of giving assent must be selected before younger children or infants, unless there are sound scientific reasons for performing the research in younger children first.

Research must always be conducted in adults before it is conducted in children if it does not include interventions and procedures that hold out the prospect of benefit to participants, as in the case of drug toxicity studies. First exploring the toxicity of new drugs in adult populations represents a way of reducing risk for children and adolescents who might be involved in subsequent investigations of the same intervention.

Minimal risk and a minor increase above minimal risk. Research risks are minimal when the risk of serious harm is very unlikely and the potential harms associated with more common adverse events are low (see guideline 6). Risks in research must be compared to risks that an average, normal, healthy child experiences in daily life or during routine examinations. If the risks are considered as minimal in these situations, they may also be considered as minimal in pediatric research (see guideline 6). A research ethics committee may permit a minor increase above minimal risk for research procedures that have no prospect of benefit when the necessary data cannot be gathered in adults and in a less risky or burdensome manner, and the social value of the research for children or adolescents is compelling. While there is no precise definition of a "minor increase" above minimal risk, the increment in risk must only be a fraction above the minimal risk threshold and considered acceptable by a reasonable person (see guideline 4).

Assent. Children and adolescents who are legal minors cannot give legally valid informed consent, but they may be able to give assent. To give assent means that the child or adolescent is engaged in the research discussion in accordance with his or her capacities. Assent must be considered as a process (see guideline 3). Furthermore, the researcher must involve the child or adolescent in the actual decision-making process and use age-appropriate information. It is of major importance to inform the child or adolescent and obtain assent as described above, preferably in writing when the child becomes literate. The process of obtaining assent must take into account not only the age of children, but also his or her individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation.

If child participants reach the legal age of majority and become capable of independent informed consent during the research, their informed consent to continued participation must be sought and their decision respected.

Deliberate objection. Some children and adolescents who are too immature to give assent may be able to register a 'deliberate objection', i.e. an expression of disapproval or refusal of a proposed procedure. The deliberate objection of an older child or adolescent, for example, is to be distinguished from the behaviour of an infant that is likely to cry or withdraw in response to almost any adverse stimulus. A deliberate objection by a child or adolescent to taking part in research must be respected even if the parents have given permission, unless the child or adolescent needs treatment that is not available outside the context of research, the research intervention has a clear prospect of clinical benefit, and the treating physician and the legally authorized representative consider the research intervention to be the best available medical alternative for the given child or adolescent. In such a case, particularly if the child is very young or immature, a parent or guardian may override the child`s objections. However, in some situations parents may press an researcher to persist with an investigational intervention against the child`s wishes. Sometimes this pressure is meant to serve the parents' interests rather than the child's. In this case, the parents must be overridden if the researcher believes it is not in the child's best clinical interest to enroll or continue study participation.

Permission of a parent or guardian. The researcher must obtain the permission of at least one parent or guardian in writing consistent with applicable laws and regulations. The age at which a child becomes legally competent to give consent differs substantially from one jurisdiction to another. Often children who have not yet reached the legally established age of consent can understand the implications of research participation and go through standard informed consent procedures; however, legally they can only assent to serve as research participants. Independent of its quality, assent is always insufficient to permit participation in research unless it is supplemented by the permission of a parent, a legal guardian or other duly authorized representative. The decision to continue or discontinue participation by children or adolescents who become legally competent during the study trumps the decision of their parents or legal guardians.

Waiver of parental permission. In certain circumstances, research ethics committees may waive parental permission. In such cases special protections must be devised to ensure that the best interests of these children or adolescents are being served. These circumstances might include cases in which permission of a parent is infeasible or undesirable. In some jurisdictions, certain individuals who are below the general age of consent are regarded as "emancipated" or "mature" minors and are authorized to consent without the agreement or even the awareness of their parents or guardians. They may be married, pregnant or be parents themselves, or they may live independently. In other cases, studies involve investigation of adolescents' beliefs and behaviour regarding sexuality or use of recreational drugs. Research may also address domestic violence, sexually transmitted diseases, pregnancy, abortion, or child abuse. In these cases parental knowledge of the subject matter may place the children or adolescents at risk of questioning, intimidation, or even physical harm by their parents. In still other cases, children or adolescents do not have a legal representative, such as orphans.

In such cases, special protections to promote the best interests of these children or adolescents must include the involvement of independent child advocates. A child may also be asked to choose a relative, trusted friend, or family physician who is not involved in the research project who might then represent the child. Independent psychological and medical support for the participating children and adolescents is another special protection, though this may be difficult to realize in some communities. In such communities the study personnel must be sufficiently qualified to help children and adolescents who need medical and psychological support.

Observation of the study by a parent or guardian. A parent or guardian who gives permission for a child or adolescent to participate in research must generally be given the opportunity, to a reasonable extent, to observe the study as it proceeds, so as to be able to withdraw the child if the parent or guardian decides it is in the child's best interests to do so.

(See also Guideline 4: *Potential benefits and risks of study participation*; and Guideline 15: *Research involving vulnerable persons.)*

Guideline 18: Women as research participants

Women have distinctive physiologies and health needs and must be included in biomedical research unless a good scientific reason justifies their exclusion. In research involving women, only the informed consent of the woman herself is required for her research participation. In no case must the permission of another person replace the requirement of individual informed consent by the woman.

Commentary on Guideline 18

General considerations. Women in many societies have been discriminated against with regard to their involvement in research. In particular, women who are biologically capable of becoming pregnant have been traditionally excluded from clinical trials of drugs, vaccines and medical devices owing to concern about undetermined risks to the fetus. Although the presumption against including women has changed in recent years, they are still excluded in many cases without adequate justification. Much remains unknown about the safety and efficacy of most drugs, vaccines, or devices used by women in medical practice, and this lack of knowledge can be dangerous.

Inclusion of women of childbearing age. A general policy of excluding from clinical studies women who are biologically capable of becoming pregnant is unjust in that it deprives them of the benefits of new knowledge derived from these studies. It is also an affront to their right of self-determination. Although women of childbearing age must be given the opportunity to participate in research, they must be informed that the research could include risks to the fetus if they become pregnant during the research (see guideline 15). When participation in research might be hazardous to a fetus or a woman if she becomes pregnant, sponsors and researchers must guarantee potential participants access to a pregnancy test and to effective contraceptive methods before the research begins. Researchers must never recruit women who might become pregnant for research that is known or likely to be hazardous when access to contraceptive methods is absent, even if the absence is due to legal or religious reasons. For women who are not pregnant at the outset of a study but who might become pregnant while they are research participants, the consent discussion must include information about terminating the pregnancy, including the circumstances in which abortion is legally permitted in that jurisdiction. Also, if the pregnancy is not terminated, participants must be guaranteed a medical follow-up for their own health and that of the infant and child.

Women who become pregnant during research. Many biomedical protocols call for stopping the participation of women who become pregnant during the research. In cases where a drug or biological product is known to be mutagenic or teratogenic, women must be removed from the study and access to diagnostic tests must be provided to reveal any fetal anomalies. If anomalies are detected, women may be referred for an abortion where it is legally available. When there is no evidence on the basis of which a potential harm to the fetus can be assumed, women who become pregnant must not automatically be removed from the study, but must be offered the option to continue or end their participation. In case the women opt for continued participation, researchers and sponsors must offer adequate monitoring and support.

Vulnerability. Some women become vulnerable in research because of heightened psychological, social, physical, or legal risks. Examples include surveys and interviews regarding intimate partner violence and rape; social and behavioral research involving sex workers or women who inject drugs; and studies that solicit information about sexual behavior. Breach of confidentiality in these types of research could result in serious harms to women, even if the only information disclosed is their participation in the research.

When women are vulnerable and potential participants in research, researchers need to exercise special care in the evaluation of risks and potential benefits as well as the informed consent process. In some cultures spouses or community leaders typically grant permission to invite women to participate. This authorization must not be used as a substitute for individual informed consent. The women must have adequate time and a proper environment in which to decide to enroll. When the research involves household surveys or interviews, researchers must take special care to ensure that the women are interviewed in a private place without the possibility of intrusion by other family members. In such studies, women must be given the option of conducting the interview in a setting of their choosing outside the home. In studies involving women who have experienced gender-based violence, participation in interviews may cause emotional distress. Researchers must be prepared with referrals for psychological counseling if the need arises.

Guideline 19: Pregnant and lactating women as research participants

Pregnant and lactating women have distinctive physiologies and health needs. Research designed to obtain knowledge relevant to the health needs of the pregnant and lactating woman must be promoted. Research in pregnant women must be initiated after careful consideration of the best available relevant data.

In no case must the permission of another person replace the requirement of individual informed consent by the pregnant or lactating woman.

For research interventions or procedures that have the potential to benefit either pregnant or lactating women or their fetus or infant, risks must be minimized and outweighed by the prospect of individual benefit.

For research interventions or procedures that have no potential benefits for participants

- **the risks must be minimized and no more than minimal; *and***
- **the purpose of the research must be to obtain knowledge relevant to the particular health needs of pregnant or lactating women or their fetuses or infants.**
- **When the social value of the research for pregnant or lactating women or their fetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-lactating women, a research ethics committee may permit a minor increase above minimal risk.**

All research involving pregnant women must include short term and long-term follow up of future children, as adverse events associated with research in pregnancy may not occur immediately.

As a general rule, health related research involving pregnant women that has the potential for serious harm to the fetus must be conducted only in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research makes the pregnancy unwanted

Commentary on guideline 19

General considerations. Physicians prescribe medications for pregnant and lactating women, but most often do so in the absence of studies involving such women and without adequate evidence of safety and efficacy. A direct consequence of the routine exclusion of pregnant women from clinical trials is their use of medications (both prescription and non-prescription) lacking data from clinical trials about the potential benefits and harms to themselves, their fetuses and their future children. Therefore, it is imperative to involve pregnant and lactating women in research to learn about the currently unknown risks and benefits to them, as well as to the fetus or nursing infant.

A case in point is the thalidomide episode, in which about 10,000 babies around the world (many in western Europe) were born with severely deformed limbs because their mothers had taken medication when pregnant. This tragedy is often cited as a reason for excluding pregnant women from biomedical research, but the lesson to be learned is the opposite. Never having been tested in pregnant women, the drug came to market and was readily available for morning sickness, a relatively mild condition. Had the drug been tested in very few women in a clinical trial, the mutagenic effect would most likely have been discovered and the total number of babies born with deformities would have been much smaller.

Research designed to obtain knowledge relevant to the health needs of pregnant and lactating women should be promoted in the following areas:

- interventions for conditions resulting from pregnancy;
- interventions for conditions that affect the general population and can be reasonably expected to be used without adequate supporting evidence during pregnancy (for example off-label use of medications);
- interventions for conditions that affect the developing fetus;

Informed consent and risks and potential benefits. The involvement of pregnant women in research is complicated by the fact that it may present risks and potential benefits to the fetus as well as to the woman and to the future person the fetus may become. Participation of lactating women in biomedical research may equally pose risks to the nursing infant. Research in pregnant and lactating women must be initiated after careful consideration of the best available data from: preclinical research in pregnant animal models, research in non-pregnant women, retrospective observational studies, and adverse events registries.

Researchers and research ethics committees must ensure that potential research participants are adequately informed about the risks to lactating women and their infants and about the risks to pregnant women (including future fertility), their pregnancies, their fetuses, and their future offspring. Disclosure must also include information about what has been done to maximize potential benefits and minimize risks (see guideline 4). Even when evidence concerning risks is unknown or controversial, this must be disclosed to the pregnant or lactating woman as part of the informed consent process. She will make the final decision about the acceptability of these risks for her and her fetus or infant. Women must also be informed that it is often difficult to determine causality in cases of fetal or infant abnormalities. Pregnant women may be recruited for research in which there is no prospect of individual benefit to them or the fetus only if the risks of the intervention are minimal. Examples include minimally invasive studies of new diagnostic techniques. In special circumstances, a minor increase above minimal risk may be acceptable.

Some research involving pregnant women may be directed at the health of the fetus. In such cases, the role of the woman remains the same: she is the decision maker for any interventions that affect her. This does not exclude the possibility of the woman consulting with the father of the fetus, if she wishes.

Especially in communities or societies in which cultural beliefs accord more importance to the fetus than to the woman's life or health, women may feel constrained to participate, or not to participate, in research. Special safeguards must be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of direct benefit to the fetus and not to the woman herself.

Researchers must include in protocols on research involving pregnant women a plan for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the infant and child.

Minimal risk and a minor increase above minimal risk. Research risks are minimal when the risk of serious harm is very unlikely and the potential harms associated with more common adverse events are low (see guideline 4). Risks in research must be compared to risks that an average, normal, healthy pregnant or lactating woman experiences in daily life or during routine examinations. If the risks are considered as minimal in these situations, they may also be considered as minimal in research involving pregnant or lactating women. A research ethics committee may permit a minor increase above minimal risk for research procedures that have no prospect of benefit when the necessary data cannot be gathered in non-pregnant or non-lactating women, and the social value of the research for pregnant or lactating women is compelling. While there is no precise definition of a "minor increase" above minimal risk, the increment in risk must only be a fraction above the minimal risk threshold and considered acceptable by a reasonable person (see guideline 4).

Serious harm and access to abortion. Research with pregnant women must be conducted only in settings where these women can be guaranteed access to a safe, legal abortion. This rule serves to prevent women from having to carry to term and deliver babies with known anomalies against their wishes. Before pregnant women are enrolled, researchers must determine whether significant fetal abnormality is recognized as an indication for abortion in that jurisdiction. If it is not, then, pregnant women must not be recruited for research in which there is a realistic basis for concern that significant fetal abnormality may occur as a consequence of participation in research. At the same time, this rule might restrict potentially valuable research in countries where women cannot be guaranteed access to abortion. In such cases research projects can be conducted only if a local research ethics committee determines that the research has compelling social value for pregnant or women and the women are informed about existing restrictions on abortion and possible options for obtaining an abortion in another country.

Guideline 20: Research in disaster situations

Disasters such as epidemics, earthquakes, tsunamis, and military conflicts can have a sudden and devastating impact on the health of large populations. In order to identify effective ways of

mitigating the health impact of disasters, health-related research must form an integral part of disaster response.

While conducting research in disasters, it is essential to uphold the ethical principles embodied in these guidelines. The importance of generating knowledge quickly and maintaining public trust, as well as the practical challenges of conducting research in a situation of crisis, need to be carefully balanced with ensuring the scientific validity and ethical conduct of studies. The conduct of research must not unduly compromise the response to the victims of a disaster.

In particular, researchers, sponsors, and research ethics committees must ensure that:

- **studies are designed so as to yield scientifically valid results under the challenging and often rapidly evolving conditions of a disaster (see guideline 1)**
- **the research is responsive to the health needs or priorities of the disaster victims and cannot be conducted outside a disaster situation (see guideline 2)**
- **participants are selected fairly and adequate justification is given if particular populations (for example health workers) are targeted (see guideline 3)**
- **burdens and benefits in the selection of groups of subjects as well as the possible benefits of the research are equitably distributed (see guideline 3)**
- **the risks and potential benefits of experimental interventions are assessed realistically, especially when they are in the early phases of development (see guideline 4)**
- **communities are actively engaged in study planning, while recognizing the associated practical challenges and ensuring cultural sensitivity (see guideline 7)**
- **the individual informed consent of participants is obtained even in a situation of duress (see guideline 9)**

Research in disasters must ideally be planned ahead. Health officials and research ethics committees must develop procedures to ensure appropriate, timely and flexible mechanisms and procedures for ethical review and oversight. For example, research ethics committees could pre-screen study protocols in order to facilitate and expedite ethical review in a situation of crisis. Similarly, researchers and sponsors could make pre-arrangements on data and sample sharing that research ethics committees review in advance.

Commentary on guideline 20

Humanitarian response and research. Disasters are sudden events that cause great suffering or loss of life. Disease and illness can either be the cause of disasters, or they can be a result from disasters of other origin. For example, epidemics can lead to disasters and destabilize political institutions or undermine economic activity. Conversely, natural and man-made disasters, such as earthquakes and war, can weaken or destroy health systems and have a devastating impact on individual and population health. The first and foremost obligation in disaster situations is to respond to the needs of those affected. At the same time, there is an obligation to conduct health-related research because disasters can be difficult to prevent and the evidence base for effectively preventing or mitigating their public health impact is limited. These two obligations can come into conflict. In particular, humanitarian response and health-related research often rely on the same infrastructure and the same personnel, so that priorities between the two may need to be set. If nurses and physicians become researchers this may also create dependent relationships (see guideline 9). Humanitarian workers, researchers and sponsors must be aware of these conflicts and ensure that their studies do not unduly compromise the disaster response. Researchers and sponsors should also aim to add to the infrastructure for the humanitarian response. Moreover, all studies must be responsive to the health needs or priorities of the affected populations, and it must not be possible to conduct the research outside a disaster situation.

General challenges in disaster research. In infectious disease outbreaks, there can be a lot of pressure to conduct research. This is especially the case when diseases have a high mortality rate and the treatment options are limited (for example 2014 Ebola outbreak). Conversely, in natural or man-made disasters, research can be met with great skepticism or even hostility. Researchers and sponsors must be equipped to negotiate these pressures in what are typically fragile political and social situations. Furthermore, disasters pose numerous challenges for conducting ethically responsible research. For example, potential study participants often suffer from serious physical or psychological trauma that can make it difficult for them to protect their rights and interests. Limited health infrastructure can require making compromises in data collection and study design. Despite these and challenges, it is essential that researchers and sponsors uphold the ethical principles embodied in these guidelines, even if the standard ways of respecting these principles may need to be modified. In fact, the disaster situation can require modifying standard procedures so that the ethical principles can be upheld in the most expedient way possible. For example, while ethical oversight is essential in all research, accelerated ethical review during disasters may be necessary to ensure that valuable ethical studies can begin as soon as possible.

While all ethical principles in this guideline have to be upheld, some require special attention.

Potential benefits and risks of investigational interventions and emergency use outside clinical trials. Especially when disasters are caused by an infectious disease that is highly contagious or serious (for example influenza, Ebola), there is great pressure to develop effective treatments and vaccines. Moreover, when facing a serious threat, many people are willing to assume high risks and use unproven agents within or outside of clinical trials. However, it is essential that researchers and sponsors realistically assess the potential benefits and risks of experimental interventions and communicate these clearly to potential participants and individuals at risk. Even under ordinary circumstances, many promising experimental agents do not prove to be safe and effective. Moreover, experimental interventions must be systematically evaluated in clinical trials. Widespread emergency use with no or limited data collection about patient outcomes must therefore be avoided.

Equitable distribution of risks and benefits. Because experimental interventions are often limited in disaster situations, fair selection of participants is essential (guideline 3 on equitable distribution). Especially in dire emergencies, well-off and well-connected patients must not be further privileged and the exclusion of vulnerable populations must be justified (guideline 15 on vulnerable persons). It may be acceptable to prioritize certain populations in study enrolment. For example, health professionals often put themselves at risk during a disaster (for example epidemic), and they could help more patients once recovered. The principles of reciprocity and helping the largest number of people could therefore justify their prioritization. At the same time, health workers are often well-off and have special ties to the medical establishment. Their priority might therefore further privilege the well-off, especially when compared to those who put themselves as risk without being trained as health professionals (for example burial teams during an epidemic). Researchers, sponsors, and Research ethics committees need to ensure that burdens and benefits in the selection of groups of subjects are equitably distributed (see guideline 1).

Scientific validity. Disasters unfold quickly and study designs need to be chosen so that studies will yield meaningful data in a rapidly evolving situation. Moreover, study designs must be feasible in a disaster situation but still appropriate to ensure the study's scientific validity. Without scientific validity, the research lacks social value and must therefore not be conducted (see guideline1 on social value). The research may even detract personnel or resources from the disaster response. In clinical trials, the randomised-controlled trial design remains the "gold standard" for collecting robust data. However, researchers, sponsors, Research ethics committees and others must explore alternative trial designs that may increase trial efficiency and access to promising experimental interventions while sufficiently maintaining scientific validity. The methodological and ethical merits of alternative trial designs must be carefully assessed before these designs are used. For example, when testing experimental treatments

or vaccines during an epidemic, the appropriate trial design will depend on the promise of the investigational agent, the variation of critical background variables (for example mortality and infection rates), and measurement and other practical challenges, among other factors. Researchers and sponsors must carefully evaluate the relative merits of different designs (for example observational or placebo-controlled) based on these factors.

Community engagement. Because disasters often lead to vulnerability and fragile political and social situations, engaging local communities about the research is essential for maintaining public trust and ensuring that studies are conducted in a culturally sensitive manner (see guideline 7 on community engagement). Researchers and sponsors can use creative mechanisms and processes to expedite and facilitate community engagement in a disaster situation (for example social media). Fostering community leadership will often be important to address distrust and effectively discuss complex and controversial issues, for example in order to gain support for the study design.

Ethical review and oversight. The standard mechanism for ethical review will often be too time consuming to enable research during disasters, and procedures to ensure appropriate, timely and flexible study protocols in order to facilitate and accelerated ethical review in a situation of crisis. However, pre-screening cannot substitute for ethical review with specific information added at the time of the ethical review oversight are therefore needed. For example, research ethics committees or a specialist ethics committee (perhaps on a national or regional level) may conduct an initial accelerated review of study protocols and continue oversight if studies raise significant ethical concerns. Research in disaster situations must be planned in advance. This can involve, among other things, submitting study protocols or protocol parts for ethical pre-screening and drafting arrangements for data and sample sharing between collaborators. Research ethics committees might thus pre-screen disaster. Health officials might also create an international network of specialists that could inform local review during a disaster.

Informed consent. Even though most disaster victims are under duress, it is important to obtain their informed consent for study participation and, in particular, emphasize the difference between research and humanitarian intervention. This is especially important in the context of clinical trials that test experimental interventions in the early phases of development. The fact that potential participants are under duress does not preclude them from making a voluntary decision (guideline 9 on informed consent). The informed consent process must be designed in a way that is comprehensible and sensitive to persons who are under duress. When information leaflets are too long, a summary must be provided (see guideline 9). Incompetent participants, for example orphans without a surrogate decision maker, are entitled to protection. Special protections for incompetent participants may apply, as described in guideline 16 in the section on *Emergency care situations in which the researcher anticipates that many participants will be unable to consent*

(See also guideline 17: Research involving children).

Guideline 21: Implementation research

Implementation research investigates an intervention previously shown to be effective in a different research setting to determine whether it can be successfully adapted to a new setting. The same ethical principles that govern all research are applicable to implementation research. However, special problems arise when a cluster randomised design is employed. In this

research design, groups of individuals (clusters) or communities are randomised to different interventions.

In advance of initiating an implementation trial, researchers, sponsors, relevant authorities, and research ethics committees must

- **determine who are the research subjects and whether informed consent must be obtained from patients, health care workers, or members of both groups in certain studies**
- **determine whether requiring informed consent and allowing refusal to consent may invalidate or compromise the research results**
- **determine whether a no-intervention group is ethically acceptable as a comparator in implementation research**
- **decide whether permission must be obtained from a gatekeeper**
- **consider the possibilities to de-implement the intervention if it turns out to be inferior than care as usual**

Commentary on guideline 21

Implementation research. Many implementation research studies involve the training of healthcare workers in diagnostic or therapeutic methods of proven efficacy elsewhere. The aim of such research is not to demonstrate efficacy but rather, to ascertain whether the healthcare workers have learned to use the technique properly. The line between implementation research and quality improvement in a health facility is often blurred. The head of a hospital or unit may decide to train physicians or nurses in order to introduce an intervention that has been proven elsewhere. In that type of quality improvement, there is typically no randomization, usually no review by a research ethics committee, and no informed consent obtained from the health care workers, who are the targets of the intervention. However, when different floors of the hospital or different health care facilities are randomised, with some getting the new training and others doing their routine procedures, the act of randomization transforms quality improvement into implementation research. It would then require review by a research ethics committee, which would have to determine whether consent is needed from patients and whether consent from health care workers may be waived.

Identifying the research participants. As in all research involving human participants, individuals who are targeted by an intervention are considered to be human subjects of research. In cluster randomised trials, the subjects can be patients, health care workers, or both. When an implementation study is conducted at a cluster level (different hospitals, clinics, or communities) it can be difficult if not impossible to obtain consent from health care workers. If some health care workers refuse to be observed or to apply a new diagnostic or therapeutic tool, that could confound the results of the research. Researchers would not be able to tell whether the intervention is sufficiently effective if some health care workers employ their usual procedures. A waiver of consent would then be an option (see guideline 4), but health care workers must nevertheless be notified that a study is taking place. If the interventions are directly carried out on patients, they would normally also be considered research subjects.

Patients may not be directly intervened upon in some implementation research but aggregate data from patients' records may be used to judge the effectiveness of the intervention. An example is the introduction of new infection control procedures for workers in one cluster, with no change in procedures for the control cluster. Because only aggregate data is recorded regarding the number of infections, no consent is required from the patients.

Informed consent. As a general rule, researchers must obtain informed consent from human research participants in implementation research using a cluster-randomised design, unless a waiver or

modification of consent is granted by a research ethics committee (see guideline 10). Waivers or modifications of informed consent may be common in cluster randomised trials because researchers may want to avoid participants in the control group learning about the intervention in the intervention group and accordingly change their behavior or try to get the intervention at another location. Another reason for the use of waivers or modifications of consent in cluster randomised trials is that it is sometimes virtually impossible to obtain individual informed consent. This occurs when the intervention is directed at an entire community, making it impossible to avoid the intervention. Examples include a study comparing methods of incinerating waste or fluoridating the drinking-water supply to prevent dental carries. Members of the intervention community cannot avoid being affected by the intervention, so obtaining individual informed consent is impossible. Similarly, if the units in a cluster are hospitals or health centers, it could be difficult for patients to find another hospital or general practice to avoid a new method of delivery of preventive services.

Although in most cluster randomised trials participants cannot consent to being randomised, depending on the type of study design they may be able to give informed consent to receive the intervention. The intervention may be delivered at the individual level while the communities to which the individuals belong are randomised at the cluster level (for example a vaccination campaign applied at the school level). These trials are called *individual-cluster randomised trials*. In some *individual-cluster randomised trials*, individuals may be able to consent to the intervention before it is administered in that cluster. For example, parents will not be able to consent to their children's school being randomised to a vaccination program or to being allocated to that cluster, but they could consent or refuse to consent to their child's vaccination at school. In cluster randomised trials it may also be the case that both the intervention and the community are randomised at the cluster level. These trials are called *cluster-cluster randomised trials* (for example all the students in a school or all residents of a community). In *cluster-cluster randomised trials* individual informed consent for receiving the intervention is typically difficult to obtain since it is almost impossible to avoid the intervention. At the same time, it is important to see that individual consent for data collection procedures is usually possible in both types of cluster randomised trials.

Ethical acceptability of a no-intervention group. By definition, implementation research investigates interventions that have been proven to be effective elsewhere. A question therefore arises whether it is ethically acceptable to withhold the proven intervention from a control group I a cluster randomised trial. This situation is analogous to that of placebo controls in a randomised, controlled trial when an established, effective prevention or treatment exists. If withholding the proven intervention from the control cluster would expose participants to more than a minor increase above minimal risk, it would be unethical to use that study design. An example would be the introduction of sterilizing equipment or disposable needles in a resource poor health center with a high infection rate among the patients. In the implementation study, health care workers would have to be educated in the use of the new equipment and instructed to throw away the disposable needles. Since the reuse of needles without sterilization would expose patients to more than a minor increase above minimal risk, it would be unethical for the control cluster to continue the usual practice. In such cases, it is necessary for researchers to explore an alternative design, such as using historical controls from the same facility. Research ethics committees have the responsibility to determine whether the proposed research is ethically acceptable when the methodology calls for withholding the established effective treatment from the control cluster.

Gatekeeping in cluster randomised trials. When a cluster randomised trials substantially affects cluster or organizational interests, and a gatekeeper (for example a community leader, headmaster, or local health council) possesses the legitimate authority to make decisions on the cluster or organization's behalf, the researcher must obtain the gatekeeper's permission to enroll the cluster or organization in the trial. Such permission does not replace the need to obtain individual informed consent where this is required. While this gatekeeper may not have been appointed or elected for the specific purpose of giving permission for the cluster to participate in research, the scope of authority must encompass

interventions of the type in question if provided outside of a research project; moreover, the decision-maker must ensure that the risks of participation in the study and the randomization are commensurate with the benefits for the cluster or for society. The gatekeeper may choose to consult a wider group of community representatives or advisers before taking the decision to permit the study.

Guideline 22: Use of online information or tools in health-related research

The ethical principles embodied in these guidelines are applicable to health-related research using online information or tools. However, such research can have unique features that require special consideration.

Commentary on guideline 22

General considerations. Information available on, or collected through, online platforms offers opportunities and challenges for health-related research. Some information is provided directly by users. For example, users of health apps, online patient groups, or health-related information sites supply health-related data to these sites or apps. Other information is generated by tracking online behavior, such as the purchase of prescription drugs through online pharmacies. Researchers may observe what online users are saying or doing without interacting directly with them. Conversely, researchers may use online tools or platforms as a way of conducting studies, such as online surveys.

Scientific validity of the research using online information or tools. One potential problem with health-related research using online information or tools is that the veracity of the data can be more difficult to confirm than in research involving face-to-face interaction. For example, respondents to an online survey may not satisfy the inclusion or exclusion criteria for the given research project. Minors might respond to studies intended to recruit adults. People can – consciously or unconsciously - pretend to be what they are not. Such responses can compromise or undermine the accuracy of online data. Therefore, researchers must discuss the validity of their data in their report.

Consent and ethical review. The context in which information is provided or obtained is important, and whether or not the consent to the use or collection of online information is acceptable depends on reasonable expectations for how this information is used in the given context. There is a relevant difference between situations in which researchers i) analyze information that is clearly publicly accessible and perceived as such, ii) analyze information that users have provided in a semi-private space, and iii) collect information specifically for research purposes.

i) Information publicly available on the internet and known to be publicly accessible by the users, meaning that researchers only observe and do not interact with human subjects. In such cases, researchers can use the information after accelerated ethical review and without individual informed consent (see guideline 4). Exemptions from ethical review may be applicable (see guideline 23).

ii) On other online platforms, a certain inner, seemingly private circle is created online, in which users reasonably expect only limited access to information. Examples are social media sites where users create an online circle of friends by invitation or users pay to join an online community that is dedicated to the exchange of health-related information. On these platforms, service providers must offer authorization mechanism such that users must be explicitly informed about the possibility that research may be done with their information and ideally similar to broad informed consent to research with biological material (see guideline 11). Users must give specific permission for such research. This explicit broad informed consent procedure must be separate from agreeing to the terms of use.

When providers of online platforms or services make user information accessible for research, it is recommended that they establish appropriate governance structures to evaluate and monitor studies on

their users' information. For example, a qualified member of staff could be charged with evaluating study protocols before granting researchers access and, where necessary, refer protocols for standard research ethics review. Researchers must make their presence explicit while conducting studies on semi-private online platforms or services, for example by posting an announcement in a "news for users" section. Researchers must not actively recruit participants for other research on these kinds of platforms unless this possibility is clearly indicated in the broad informed consent.

iii) When researchers use online tools to collect data specifically for research purposes, such as online surveys, these studies must undergo ethical review, consistent with national legislation or regulations, just like other research. In order to protect confidentiality, survey participants could be advised to adopt a fictional name. When researchers use online tools to actively recruit participants for their research, a user must receive information on research participation with specific options relevant to his or her situation and informed consent must be sought. Exemptions from review may be applicable (see guideline 23).

Data management. Participants' privacy, confidentiality and other interests can be at stake when data are conveyed to others electronically. Researchers must make sure that confidentiality of information is guaranteed during data collection, storage and sharing (see guideline 24 on public accountability) and the combination of databases. Registration forms and questionnaires with personal identifiers must receive a high degree of security. Researchers and sponsors must use secure passwords and the best available encryption technology in order to ensure that only authorized persons are able to access the data (see guideline 12).

Public accountability. After completion of a study, the accuracy and completeness of the information made available on the Internet become relevant. Researchers must be explicit in indicating whether the information provided is preliminary or final and indicate the date of uploading the data (see also guideline 24).

Guideline 23: Requirements for establishing research ethics committees and their review of protocols

All proposals to conduct health-related research involving humans must be submitted to a research ethics committee to review their ethical acceptability, unless there are exemptions as specified by applicable law or regulations. The researcher must obtain approval or clearance by such a committee before beginning the research. The research ethics committee must conduct further reviews as necessary, in particular if there are significant changes in the protocol.

Research ethics committees must review research protocols according to the principles set out in these guidelines.

Research ethics committees must be formally established and given adequate mandate and support to ensure timely and competent review according to clear and transparent procedures. **Committees must include multidisciplinary membership in order to competently review the**

proposed research. Committee members must be duly qualified and regularly update their knowledge of ethical aspects of health-related research. Research ethics committees must have mechanisms to ensure independence of their operations.

Research ethics committees from different institutions or countries must establish efficient communication in cases of externally sponsored and multi-center research. In externally sponsored research, appropriate ethical review take place in both the host and the sponsoring community.

Research ethics committees must have a clear procedure for researchers or sponsors to make legitimate appeals to the decisions of research ethics committees.

Commentary on Guideline 23

General considerations. Research ethics committees may function at the institutional, local, regional, or national level, and in some cases at the international level. They must be established in accordance with rules set by a national or other recognized authority. Regulatory or other governmental authorities must promote uniform standards for committees within a country. Research institutions and states must allocate sufficient resources for the ethical review process. Contributions of study sponsors to institutions or governments in order to support ethics review must be made in a transparent process. Under no circumstances may payment be offered or accepted to procure a committee's approval or clearance of a protocol.

Scientific and ethical review. Although in some instances scientific review precedes ethical review, research ethics committees must always have the opportunity to combine scientific and ethical review in order to ensure the social value of the research (guideline 1). The ethical review must consider, among other aspects, the study design, provisions for minimizing risk and that any remaining risks are appropriately balanced in relation to the potential benefits for participants and the social value of the research, issues of safety (safety of the study site and medical interventions and monitoring safety during the study), and the feasibility of the research. Scientifically unsound research involving human subjects is unethical in that it may expose them to risk or inconvenience for no purpose. Even if there is no risk of injury, involving subjects' and researchers' time in unproductive activities wastes valuable resources. Research ethics committees must therefore recognize that the scientific validity of the proposed research is essential for its ethical acceptability. Committees must either carry out a proper scientific review, verify that a competent expert body has determined the research to be scientifically sound, or consult with competent experts to ensure that the research methods are appropriate. If research ethics committees do not have expertise to judge science or feasibility, they must draw on relevant expertise.

Accelerated review. Accelerated review is a process by which studies that involve no more than minimal risk may be reviewed and approved in a timely manner by an individual research ethics committee member or a designated subset of the full committee. Relevant authorities or research ethics committees may establish procedures for the accelerated review of research proposals. These procedures should specify the following:

- the nature of the applications, amendments, and other considerations that will be eligible for accelerated review;
- the minimum number of research ethics committee members for accelerated review;
- the status of decisions (for example, subject to confirmation by a full research ethics committee or not).

Relevant authorities or research ethics committees must establish a list of criteria for protocols that qualify for an accelerated review process.

Further review. The research ethics committee must conduct further reviews of approved studies as necessary, in particular if there are significant changes in the protocol that could impact the validity of the consent, the safety of participants, or other ethical matters that emerge during the course of the study. These further reviews include progress reports and possible monitoring of researchers' compliance with approved protocols.

Committee membership. The research ethics committee must be constituted according to a document that specifies the manner in which members and the chair will be appointed, reappointed, and replaced. Research ethics committees must have members capable of providing competent and thorough review of research proposals submitted to them. Membership normally must include physicians, scientists and other professionals such as research coordinators, nurses, lawyers, and ethicists, as well as (lay) persons who can represent the cultural and moral values of the community. Committees must include both men and women. When a proposed study involves vulnerable individuals or groups, as may be the case in research involving prisoners or illiterate persons, representatives from appropriate advocacy groups must be invited to meetings where such protocols will be reviewed (see guideline 15). Regular rotation of members is desirable for balancing the advantage of experience with that of fresh perspectives.

Members of research ethics committees must regularly update their knowledge about the ethical conduct of health-related research. If committees do not have the relevant expertise to adequately review a protocol, they must consult with external persons with the proper skills or certification. Research ethics committees must keep records of their deliberations and decisions.

Conflicts of interests from research ethics committee members. Research ethics committees must have mechanisms to ensure the independence of their operations. In particular they must avoid any undue influence and minimize and manage conflicts of interests. Research ethics committees must require that their members disclose to the committee any interests they may have that could constitute a conflict of interest or otherwise bias their evaluation of a research proposal. Research ethics committees must evaluate each study in light of any disclosed interests and ensure that appropriate steps are taken to mitigate possible conflicts of interest (see guideline 25 on conflicts of interest). Research ethics committees may receive a fee for reviewing studies. This does not necessarily create a conflict of interest (see guideline 25).

National (centralized) or local review. Research ethics committees may be created under the aegis of national or local health administrations, national (or centralized) medical research councils or other nationally representative bodies. In a highly centralized administration a national, or centralized, review committee may be constituted for both the scientific and the ethical review of research protocols. In countries where medical research is not centrally administered, ethical review can also be undertaken at a local or regional level. Whether research is nationally or locally reviewed varies per country and may depend on the size of the country and the type of the research. The authority of a local research ethics committee may be confined to a single institution or may extend to all institutions in which biomedical research is carried out within a defined geographical area or network.

Externally sponsored research. Research may be externally sponsored, meaning that that it is sponsored, financed, and sometimes wholly or partly carried out by an external organization with the collaboration or agreement of the appropriate authorities of the host community. External sponsors must collaborate with local partners (see guideline 8).

Externally sponsored research must be reviewed at the site of the sponsor as well as locally. Local committees must be fully empowered to disapprove a study that they believe to be unethical.

Multi-centre research Some research projects are designed to be conducted in a number of centres in different communities or countries. To ensure that the results will be valid, the study must be conducted in a methodologically identical way at each centre. However, committees at individual centres must be authorized to make changes to a template of the informed consent document provided by the sponsor of the lead institution in the multi-centre trial.

To avoid lengthy procedures, multi-centre research in a single jurisdiction should be reviewed by one research ethics committee only. In cases of multi-centre research, if a local review committee makes changes to the original protocol that they believe are necessary to protect the research participants, these changes must also be reported to the research institution or sponsor responsible for the whole research program for consideration and due action. This is to ensure that all other subjects can be protected and that the research will be valid across sites.

Ideally review procedures are harmonized, which may decrease the time needed for review and accordingly speed up the research process. In order to harmonize review processes and to maintain sufficient quality of these processes, ethics committees must develop quality indicators for ethical review. Appropriate review has to be sensitive to increases in risk of harm or wrong to local participants and populations. To ensure the validity of multi-centre research, explicit inter-centre comparability procedures must be introduced for changes made in the protocol.

Exemptions from review. Internet research (see guideline 22) or some epidemiological studies may be exempt from ethical review if publicly available data is analyzed or the data for the study are generated by observation of public behavior, provided that in doing so or in reporting results, data about individual persons or groups of persons is anonymized or coded. Health systems research studies may be exempted from review if public officials are interviewed in their official capacity on issues that are in the public domain.

Protocol amendments, deviations, violations and sanctions. During the study deviations from the original study might occur, such as changes in the sample size or analysis of the data as described in the protocol. Deviations must be reported to research ethics committees. In the case of permanent deviations researchers may write an amendment. The research ethics committee must then decide whether a deviation is legitimate or illegitimate. Deviations are therefore not always protocol violations. Protocol violations are deviations from the original protocol that significantly affect the rights or interests of research participants and/or significantly impact the scientific validity of the data.

Apart from protocol violations, a researcher may also fail to submit a protocol to a research ethics committee. This omission must be considered a clear and serious violation of ethical standards, unless applicable regulations specify conditions for exemptions from review.

Research ethics committees generally have no authority to impose sanctions on researchers for protocol violations or violations of ethical standards in the conduct of research involving humans. However, committees may halt the continuation of a previously approved protocol if it finds protocol violations or other misconduct on the part of researchers. Committees must report to institutional or governmental authorities any serious or continuing non-compliance with ethical standards in the conduct of previously approved research projects.

Guideline 24: Public accountability for health-related research

In order to promote societal trust in health-related research, researchers, sponsors, research ethics committees, editors and publishers have an obligation to ensure public accountability for research and its results. In particular, researchers must prospectively register their studies, publish the results and share the data on which these results are based in a timely manner. Negative and inconclusive as well as positive results of all studies must be published or otherwise be made publicly available.

Commentary on guideline 24

General considerations. It is in the interest of all to improve the effectiveness of health care and public health to attain their fundamental goals: to prevent and cure disease where possible and otherwise alleviate pain and suffering (see guideline 1). Health-related research plays a vital role in this and therefore it is in the interest of society to promote such research for the benefit of all. At the same time, health-related research comes with risks and burdens for participants and with professional or financial benefits for the researchers and sponsors. Health-related research only functions in the presence of professional and public trust. Trust can be enhanced by ensuring public accountability for research and its results. Therefore, researchers, sponsors, research ethics committees, editors and publishers all have ethical obligations with regard to the public accountability of research. This materializes in the obligations to prospectively register studies, publish their results, and share the data on which these results are based.

Trial registries. An estimated half of clinical trials are never published, and those with negative or unpromising results are more likely to disappear (a phenomenon called 'publication bias.') These unpublished data may contain important information on harms or side effects, clues about failed studies or unpromising interventions that must not be re-tested, and information that other researchers could use to increase the quality of research findings. As a first measure towards public accountability, researchers and sponsors therefore have an obligation to register their studies before they actually start, thus enabling others to see what is going on and make inquiries if reports fail to come out of the study.

Prospective registration of clinical trials enables comparison of data reported with hypotheses the protocol was initially designed to test and help to establish the number of times a hypothesis has been tested so that trial results can be understood in a broader context.

Publication and dissemination of the results of research. A next step in achieving accountability is publication and dissemination of the results of studies. Researchers have a duty to make the results of their health-related research publicly available and are accountable for the completeness and accuracy of their reports. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. In journal publications, all involved parties must adhere to the accepted guidelines (such as ICMJE) for ethical reporting. Sources of funding, institutional affiliations and conflicts of interest must be disclosed in the publication. Reports of research not in accordance with the recognized guidelines must not be accepted for publication. Sponsors must not prevent researchers from publishing unwelcome findings that restrict their freedom of publication. As the persons directly responsible for their work, researchers must not enter into agreements that interfere unduly with their access to the data or their ability to analyze the data independently, prepare manuscripts, or publish them. Researchers must also communicate the results of their work to a lay audience. Researchers should ideally promote and enhance public discussion.

Data sharing There are compelling reasons to share the data of health-related research. Responsible sharing of clinical trial data serves the public interest by strengthening the science that is the foundation

of safe and effective clinical care and public health practice. Sharing also fosters sound regulatory decisions, generates new research hypotheses, and increases the scientific knowledge gained from the contributions of clinical trial participants, the efforts of clinical trial researchers, and the resources of clinical trial funders. Data sharing involves more than sharing a summary of trial results, which is already expected in publications (see above).

Data sharing requires careful balancing of competing considerations. Sharing of study data presents risks, burdens, and challenges as well potential benefits for various stakeholders. When sharing data, researchers must respect the privacy and consent of study participants. Researchers want a fair opportunity to publish their analyses and receive credit for carrying out studies and collecting data. Other researchers want to analyze data that would otherwise not be published in a timely manner and to replicate the findings of a published paper. Sponsors want to protect their intellectual property and commercially confidential information and allow a quiet period to review marketing applications. All stakeholders want to reduce the risk of invalid analyses of shared data.

What is crucial is to create a culture of responsible data sharing and mutually reinforcing incentives for sharing. Funders and sponsors must require funded researchers to share study data and provide appropriate support for sharing. Researchers and sponsors must share data and design and carry out future studies assuming that data will be shared. Research institutions and universities must encourage researchers share data. Medical journals should require that authors share the analytic data set supporting publications of study results. Patient advocacy organizations should consider data sharing plans as a criterion for funding grants and promoting studies to their constituents. Regulatory agencies around the globe should harmonize requirements and practices for data sharing. The risks of data sharing may be mitigated through controls over with whom the data are shared and under what conditions, without compromising the scientific usefulness of the shared data. Organizations that share data should make use of data use agreements, observe additional privacy protections beyond de-identification and data security as appropriate, and appoint an independent panel that includes members of the public to review data requests. These safeguards must not unduly impede access to data.

Guideline 25: Conflicts of interest

The primary goal of health-related research is to generate, in ethically appropriate ways, the knowledge necessary to promote people's health. However, researchers, research institutions, sponsors, research ethics committees, and policy-makers can have secondary interests (for example in scientific recognition or financial gain) that can conflict with the ethical conduct of research. Such conflicts between the primary goal of health-related research and secondary interests are defined as conflicts of interest.

Conflicts of interest can influence the choice of research questions and methods, recruitment and retention of participants, interpretation and publication of data, and the ethical review of research. It is therefore necessary to develop and implement policies and procedures to identify, mitigate, eliminate, or otherwise manage such conflicts of interest.

Research institutions, researchers and research ethics committees must take the following steps:

- **Research institutions must develop and implement policies and procedures to mitigate conflicts of interest and educate their staff about such conflicts.**
- **Researchers must ensure that the materials submitted to a research ethics committee include a disclosure of interests that may affect the research.**
- **Research ethics committees must evaluate each study in light of any disclosed interests and ensure that appropriate means of mitigation are taken in case of a conflict of interest.**

- **Research ethics committees must require their members to disclose their own interests to the research ethics committee and take appropriate means of mitigation in case of a conflict of interest (see guideline 23 on research ethics review)**

Commentary on guideline 25

General considerations. A conflict of interest exists when there is a substantial risk that secondary interests of one or more stakeholders in research unduly influence their judgment and thereby compromise or undermine the primary goal of research. For example, a researcher may have a financial stake in the outcomes of her study that creates a financial conflict of interest. Given the competitive environment for academic researchers and the increasing commercialization of research, managing conflicts of interests is essential for safeguarding the scientific integrity of research and protecting the rights and interests of study participants. The commentary first explains conflicts of interests and then discusses their management.

Conflicts of interest. Different stakeholders in research can have different types of conflicts of interest.

1) *Researchers*. Academic conflicts of interest can arise when researchers – or senior members of a research team – become too invested in their own ideas. For example, a researcher who has worked for decades on an investigational HIV drug may find it difficult to stop a trial early when interim results clearly recommend this course of action. Furthermore, researchers' careers depend on publishing interesting results--for instance, when applying for research funding or promotion. This can create professional conflicts of interests.

   Some researchers also have personal financial conflicts of interest. For example, researchers sometimes receive part of their salary or a "finder's fee" for recruiting research participants. When this income reflects a fair compensation for their time spent on recruitment, it does not present an inherent conflict of interest. However, a salary or "finders fee" may lead researchers – intentionally or unintentionally – to interpret the inclusion or exclusion criteria of studies too flexibly, thereby potentially exposing participants to excessive risks or compromising the scientific validity of the research. This situation raises particular concern when participants are dependent on the researcher who also is their clinician (see guideline 3 on dependent relationships), and when the salary of the clinician is considerably lower as compared to that of the researcher. It may also lead to researchers to exert pressure on eligible participants to enroll, thus compromising or undermining participants' voluntary consent. In addition, financial conflicts of interest can arise when researchers or senior members of the research team (or their close family members) have a financial stake in the sponsor of the research, such as an equity interest.

2) *Research institutions (for example universities, research centres, or pharmaceutical companies)*. Research institutions can have both reputational and financial conflicts of interests. For example, universities rely on the reputation of their research to attract faculty, students, or external funding. Some universities also patent the discoveries of their staff. Institutional conflicts of interest can also arise when a research centre derives substantial support (perhaps covering years of funding) from a single sponsor or a handful of sponsors.

3) *Research ethics committees*. Researchers often serve as members of research ethics committees and conflicts of interest can arise in this role. For example, a researcher may submit her own study protocol for review, or she may be reviewing the work of colleagues whom she knows personally, or whose work she considers critical for the success of her institution.

Research ethics committees may also have financial interests when they are directly funded by sponsors or serve an institution that significantly depends on support from a single sponsor or several sponsors.

The fact that a research ethics committee (or the institution where it operates) is paid a fee for reviewing a study does not present an inherent conflict of interest, provided that the fee is established by a general policy, reasonably related to the costs of conducting the review and is not dependent on the outcome of the review (see guideline 23 on research ethics committees).

In order to evaluate the seriousness of a conflict of interest, and to determine appropriate measures for its management, research ethics committees need to judge the risk that a secondary interest of one or more stakeholders in a study unduly compromises or undermines its ethical conduct. This involves judging both the likelihood that a secondary interest might compromise the rights or welfare of participants or the scientific validity of the research, as well as judging the magnitude of the secondary interest relative to the stakeholder's personal situation. For example, an early-career researcher with a modest salary might have more significant academic and financial conflicts of interest than an established senior member of the research team. Research ethics committees will have to exercise their judgment when evaluating the seriousness of conflicts of interest. As a general rule, a serious conflict of interest exists when there is a significant likelihood that a professional, academic, or financial interests will result in biased study results or cause important harm or wrong to participants.

Of note, conflicts of interests can influence stakeholders in the research subconsciously. For example, a researcher with a financial stake in a study may not intentionally manipulate his/her research findings. However, his/her financial interests may subconsciously influence her analysis and interpretation of the research data.

Management of conflicts of interest. All stakeholders in research share responsibility for developing and implementing policies and procedures to identify, mitigate, eliminate, or otherwise manage conflicts of interest. Although a joint responsibility, research institutions play a critical role in creating an institutional culture that takes conflicts of interest seriously and adopts appropriate measures for their management. Measures for managing conflicts of interest must be proportionate to their seriousness. For example, a minor conflict of interest may be appropriately managed by disclosure, while a serious conflict can, in rare cases, justify excluding a researcher from the study team. Policies and measures for managing conflicts of interest must be transparent and actively communicated to those affected.

1) *Education of researchers and research ethics committees*. Raising awareness of conflicts of interest, as well as the importance of managing such conflicts, is essential for effective conflict of interest procedures and policies.

2) *Disclosure of interests to research ethics committees*. Researchers must disclose conflicts of interest on their part to the ethical review committee or to other institutional committees designed to evaluate and manage such conflicts. Researchers will most likely come to recognize conflicts of interest if they are prompted to scrutinize these conflicts as an expected part of preparing a description of their projects for ethical review. Thus, the development of a standardized disclosure form and related educational and explanatory materials (by a committee or group of committees, such as a research ethics association) is recommended to ensure that researchers understand conflicts of interest and routinely report relevant facts about their own studies to research ethics committees. It is important that disclosure forms provide a definition of conflicts of interest and help researchers to understand that a conflict of interest is not necessarily

disqualifying, but may be managed. When research ethics committees have credible evidence about serious conflicts of interest related to a study that are not disclosed in the protocol, research ethics committees should contact the principal researcher for further information.

3) *Disclosure of interests to participants*. Researchers may propose, and research ethics committees may require, managing conflicts of interest by disclosing them to potential study participants in the informed consent discussion and documents (for example stock ownership). The disclosure must allow potential participants to judge the seriousness of the conflict of interest. This goes beyond describing "the nature and sources of funding for the research", which is an element of informed consent (see Appendix xxx). In the case of serious conflicts of interest, studies suggest that disclosure works best when it is provided by a health professional that is independent of the study team and potential participants are given time to reflect.

4) *Mitigation of conflicts*. Research ethics committees may consider a range of other measures to mitigate or manage conflicts of interest beyond disclosing these conflicts to potential participants. For example, where appropriate, research ethics committees may require a member of the study team who has no leading role in its design to obtain the informed consent of potential participants. Research ethics committees may also require limiting the involvement of researchers in a study when they have a serious conflict of interest. For instance, a researcher with a serious conflict may only be involved as a consultant for specific tasks that require her expertise, but not as a principal researcher or co-researcher. Alternatively, research ethics committees may require independent monitoring and review of studies where, for reasons of expertise, the full involvement of researchers with a serious conflict of interest is necessary. In cases where a serious conflict of interest cannot be adequately mitigated, research ethics committees may decide not to approve a study. Research ethics committees themselves must employ similar measures to identify, mitigate and manage the conflicts of interests of their own members. When necessary, research ethics committees may require members with a serious conflict to withdraw from deliberations of the research ethics committee and its decisions (see guideline 23 on research ethics committees).

See also guideline 4: *potential benefits and risks*, guideline 8 on *collaborative partnership*, guideline 9: *individual informed consent*; guideline 23 on *research ethics committees and review* and guideline 24 on *public accountability*