

International Ethical Guidelines for Health-related Research Involving Humans

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目录

1. 研究的科学和社会价值以及尊重受试者的权利	1
2. 低资源环境中进行的研究	3
3. 选择研究受试人群：利益与负担的公平分配	7
4. 潜在的个人利益与风险	9
5. 临床研究对照的选择	15
6. 受试者健康需求的医疗护理	21
7. 社区参与	25
8. 研究与伦理审查的合作伙伴和能力建设	29
9. 能够给予知情同意的个人	33
10. 知情同意的变更与豁免	37
11. 生物材料及相关数据的采集、存储和使用	41
12. 健康相关研究数据的采集、存储和利用	47
13. 给受试者的报销和补偿	53
14. 研究相关损害的医疗和补偿	55
15. 涉及弱势群体或个人的研究	57
16. 涉及无知情同意能力的成人的研究	61
17. 涉及儿童和青少年的研究	65
18. 妇女作为研究受试者	69
19. 孕妇和哺乳妇女作为研究受试者	71
20. 灾难和疾病暴发的研究	75
21. 组群随机试验	79
22. 健康相关研究利用网络环境和数码工具获取的数据	83
23. 组建研究伦理委员会以及审查方案的要求	87
24. 健康相关研究的公开责任	91
25. 利益冲突	95
26. 附录 1 涉及人的健康相关研究方案（或附属文件）应包括的条款	99
27. 附录 2 获取知情同意：前瞻性研究的基本信息	103

GUIDELINE 1:

SCIENTIFIC AND SOCIAL VALUE AND RESPECT FOR RIGHTS

The ethical justification for undertaking health-related research involving humans is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health. Patients, health professionals, researchers, policy-makers, public health officials, 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, sponsors, research ethics committees, and health authorities, must ensure that proposed studies are scientifically sound, build on an adequate prior knowledge base, and are likely to generate valuable information.

Although scientific and social value are the fundamental justification for undertaking research, researchers, sponsors, research ethics committees and health authorities have a moral obligation to ensure that all research is 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. Scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment, or injustice.

Commentary on Guideline 1

General considerations. In order to be ethically permissible, health-related research with humans, including research with samples of human tissue or data, must have social value. The scientific and social value of research can be difficult to quantify, but it is generally grounded in three factors: the quality of the information to be produced, its relevance to significant health problems, and its contribution to the creation or evaluation of interventions, policies, or practices that promote individual or 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.

Social value. Social value refers to the importance of the information that a study is likely to produce. Information can be important because of its direct relevance for understanding or intervening on a significant health problem or because of its expected contribution to research likely to promote individual or public health. The importance of such information can vary depending on the significance of the health need, the novelty and expected merits of the approach, the merits of alternative means of addressing the problem, and other considerations. For example, a well-designed, late phase clinical trial could lack social value if its endpoints are unrelated to clinical decision-making so that clinicians and policy-makers are unlikely to alter their practices based on the study's findings.

Similarly, although replication serves an important role in scientific research, well-designed studies that lack sufficient novelty may also lack social value.

Researchers, sponsors, research ethics committees and relevant health authorities, such as regulators and policy-makers, must ensure that a study has sufficient social value to justify its associated risks, costs and burdens. In particular, there must be sufficient social value to justify risks to participants in studies that lack the prospect of potential individual benefit to them (see Guideline 4 – Potential individual benefits and risks of research).

Scientific value. Scientific value refers to the ability of a study to produce reliable, valid information capable of realizing the stated objectives of the research. The requirement of scientific value 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 patients, clinicians, researchers, policy-makers, industrial sponsors and others) rely on the information that research generates to make decisions that have important consequences for individual and public health. For example, 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 are relevant for clinical decision-making, health and social policy, or resource allocation. Ensuring that studies uphold high scientific standards is essential for maintaining the integrity of the research enterprise and its ability to fulfil its social function.

Although the quality of the information produced by research depends critically on the scientific value of a study, scientific value alone does not make a study socially valuable. For example, a study can be rigorously designed but lack social value when the research question has been successfully addressed in prior research. However, a study cannot be socially valuable without appropriate and rigorous research methods to address the question at hand. In other words, scientific value is a necessary but not a sufficient condition for the social value of health research.

Qualification of research personnel. Sponsors, researchers, and research ethics committees must ensure that all research personnel are qualified by virtue of their education and experience to perform competently and with integrity. This includes receiving appropriate ethics education and training. Qualifications of research personnel must be adequately described in the materials submitted to the research ethics committee (Appendix I).

Respect for rights and welfare. Although the social value of research is a necessary condition for its ethical acceptability, it is not sufficient. 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 choosing whose health needs are investigated; how risks, burdens, and anticipated benefits of individual studies are distributed; and who will have access to any resulting knowledge and interventions. These and other ethical aspects of research are discussed in the following guidelines and 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. Dissemination is essential to achieving social value. The importance of disseminating scientific information, including negative findings, is discussed in Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols.

GUIDELINE 2:

RESEARCH CONDUCTED IN LOW-RESOURCE SETTINGS

Before instituting a plan to undertake research in a population or community in low-resource settings, 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, and researchers must also:

- ▶ **make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity. In some cases, in order to ensure an overall fair distribution of the benefits and burdens of the research, additional benefits such as investments in the local health infrastructure should be provided to the population or community; and**
- ▶ **consult with and engage communities in making plans for any intervention or product developed available, including the responsibilities of all relevant stakeholders.**

Commentary on Guideline 2

General considerations. This Guideline pertains to settings in which resources are so limited that the population may be vulnerable to exploitation by sponsors and investigators from wealthier countries and communities. The ethical standards applied should be no less stringent than they would be for research carried out in high-resource settings. To ensure that people in low-resource settings receive equitable benefit from their participation in health-related research, this Guideline demands that local social value be created. Low-resource settings should not be interpreted narrowly as low-resource countries. These settings might also exist in middle- and high- income countries. Moreover, a setting can change over time and no longer be considered low-resource.

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 health 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 health 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. If the knowledge to be gained from the research is intended for use primarily for the benefit of populations other than those involved in the research, the responsiveness requirement is violated. In such cases, the research raises serious concerns about justice, which requires a fair distribution of the benefits and burdens of research (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research).

Some research is intended to generate information relevant to the health needs of people in low-resource settings but is not carried out in populations that are the intended beneficiaries of the research. As an exception to the general rule specified in this Guideline, such studies can be justified because the effort to generate information relevant to significant health needs of people in low-resource settings represents an important demonstration of solidarity with burdened populations. For example, during the Ebola outbreak of 2014, phase one studies on investigational Ebola vaccines were carried out in low-resource communities not experiencing an Ebola outbreak.

Responsibilities and plans. When the research has important potential individual 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 persons are drawn, patent-holders if they are other than the sponsor, and nongovernmental 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. When applicable, it must also consider 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. The ability of the local health-care infrastructure to be able to provide the intervention must be facilitated at the outset so that delivery is possible following the completion 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 them and products are reasonably priced. Post-trial access plans are of particular concern for research conducted in low-resource settings where governments 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 should be implemented as soon as feasible. An example is the introduction of male circumcision in countries with a high burden of HIV disease. Research demonstrated a significant preventive effect of male circumcision, following which, programmes 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. To that end, agreement must be reached with the local community about the form such dissemination

should take. One example might be a study that learns why a health condition such as neural tube defects is prevalent in a particular population. Another example could be a study that results in knowledge to educate the population about foods to eat or avoid in order to promote or maintain health.

These requirements for post-trial availability to communities and populations must not be construed as precluding studies designed to evaluate novel therapeutic concepts. An example might be research designed to obtain preliminary evidence that a drug or a class of drugs is beneficial in treating a disease that occurs only in low-resource settings, 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 would be made reasonably available at its conclusion.

Additional benefits to the population or community. Benefits other than those associated with study participation 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 should 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 contributions that research or research partnerships make to the overall scientific environment of such countries and communities.

Community engagement. From the inception of research planning, it is important to ensure full participation of communities in all steps of the project, including discussions of the relevance of the research for the community, its risks and potential individual benefits, and how any successful products and possible financial gain will be distributed, for example through a benefit-sharing agreement. This consultation should 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. Research ethics committees should require community members to disclose any conflicts of interests (see Guideline 25 – Conflicts of interest). Active community involvement helps to ensure the ethical and scientific quality and successful completion of proposed research. In addition, it helps the research team to understand and appreciate the research context, 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 7 – Community engagement).

GUIDELINE 3:

EQUITABLE DISTRIBUTION OF BENEFITS AND BURDENS IN THE SELECTION OF INDIVIDUALS AND GROUPS OF PARTICIPANTS IN RESEARCH

Sponsors, researchers, governmental authorities, research ethics committees and other stakeholders must ensure that the benefits and burdens of research are equitably distributed. Groups, communities and individuals invited to participate in research must be selected for scientific reasons and not because they are easy to recruit because of their compromised social or economic position or their ease of manipulation. Because categorical 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 any knowledge gained from the research should not bear a disproportionate share of the risks and burdens of research participation. Groups that are under-represented in medical research should be provided appropriate access to participate.

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 bears 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, the criteria for unequal distribution should be scientifically and ethically justified rather than arbitrarily or conveniently chosen. Situations where unequal distribution of benefits would be considered are those in which the research particularly affects the population under study. In general, equitable distribution requires that participants be drawn from the qualifying population in the geographic area of the study where the results can be applied (see Guideline 2 – Research conducted in low-resource settings). Inclusion and exclusion criteria should not be based upon potentially discriminatory criteria, such as race, ethnicity, economic status, age or sex, unless there is a sound ethical or scientific reason to do so. For example, in cases where the under-representation of particular groups results in or perpetuates health disparities, equity may require special efforts to include members of those populations in research (see Guideline 17 – Research involving children and adolescents, Guideline 18 – Women as research participants, and Guideline 19 – Pregnant women and breastfeeding women as research participants).

Fair distribution of research benefits. Equity in the distribution of the benefits of research requires that research not disproportionately focus on the health needs of a limited class of people, but instead aims to address diverse health needs across different classes or groups. In the past, groups considered vulnerable were excluded from participation in research because it was considered the most expedient way of protecting those 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 that afflict such groups is limited. This has resulted in a serious injustice. Since information about the management of diseases is considered a benefit to society, it is unjust to intentionally deprive specific groups 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 are exposed to risks and burdens in order to generate the knowledge needed to protect and promote people's health (see Guideline 1 – Scientific and social value and respect for rights). Equity in the distribution of burdens of research requires special care to ensure that individuals, communities or populations that are already disadvantaged or marginalized are not over-represented in research. A disproportionate selection of disadvantaged or convenient populations is morally problematic for several reasons. First, it is unjust to selectively invite 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 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. Furthermore, research results obtained from disadvantaged populations may not be appropriately extrapolated to the general population.

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

Not only may certain groups within a society be inappropriately over-used as research participants, but also entire communities or societies may be over-used. Such over-use is especially problematic 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.

GUIDELINE 4:

POTENTIAL INDIVIDUAL BENEFITS AND RISKS OF RESEARCH

To justify imposing any research risks on participants in health research, the research must have social and scientific 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 potential individual benefit and the social and scientific value of the research.

The potential individual benefits and risks of research must be evaluated in a two-step process. First, the potential individual benefits and risks of each individual research intervention or procedure in the study must be evaluated.

- ▶ For research interventions or procedures that have the potential to benefit participants, risks are acceptable if they are minimized and outweighed by the prospect of potential 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 a placebo may be used are spelled out in Guideline 5 – Choice of control in clinical trials.
- ▶ For research interventions or procedures that offer no potential individual benefits to participants, the risks must be minimized and appropriate in relation to the social and scientific 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 individual 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 and scientific value of the research is compelling (see Guideline 16 – Research involving adults incapable of giving informed consent, and Guideline 17 – Research involving children and adolescents).

In a second step, the aggregate risks and potential individual benefits of the entire study must be assessed and must be considered appropriate.

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

- ▶ **The potential individual benefits and risks of research studies must be evaluated in consultation with the communities to be involved in the research (see Guideline 7 – Community engagement).**

Commentary on Guideline 4

General considerations. 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” refers to the objects 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-related behaviours. The term “procedure” refers to research activities that provide information about the object of study, for example the safety and efficacy of a new therapy. Procedures include surveys and interviews, clinical exams, monitoring (for example, an electrocardiogram), blood draws, biopsies, imaging, as well as methods used in the conduct of the research, such as randomization.

Many research interventions and procedures pose risks to participants. Risk is generally understood as an estimate 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 harm. This understanding of risk implies that discomfort, inconvenience or burdens are harms of a very small magnitude that are almost certain to occur. The ethical justification for exposing participants to risks is the social and scientific value of research, namely the prospect of generating the knowledge and means necessary to protect and promote people’s health (see Guideline 1 – Scientific and social value and respect for rights). However, some risks cannot be justified, even when the research has great social and scientific value and adults who are capable of giving informed consent would give their voluntary, 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 effective 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 are reasonable in light of the social and scientific value of the research, and that the study does not exceed an upper limit of risks to study participants.

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 individual benefits. The steps outlined in this Guideline are intended to ensure protection of the rights and welfare of study participants.

It is important to evaluate the potential individual benefits and risks of proposed research in consultation with the communities to be involved in the research (see Guideline 7 – Community engagement). This is because a community’s values and preferences are relevant in determining what constitute benefits and acceptable risks. Evaluating risks and potential individual benefits also requires a good understanding of the context in which a study is to be conducted. This is best obtained in consultation with communities. Moreover, the risk-benefit ratio of a study can change as it progresses. Researchers, sponsors and research ethics committee should therefore re-evaluate the risks and potential individual benefits of studies on a regular basis.

Evaluation of individual research interventions and procedures. To evaluate the risks and potential individual benefits of a research study, researchers, sponsors, and research ethics committees must first assess the risks and potential individual benefits of each individual research intervention and procedure, and then judge the aggregate risks and potential individual benefits of the study as a whole. Taking these successive steps is important because overall judgments of the risk-benefit profile of a study as a whole are more likely to be inaccurate because they may miss

concerns raised by individual interventions. For example, a study may involve research procedures that do not pose significant risks, yet the procedures fail to yield important information. Global risk-benefit judgments would likely miss this concern. In contrast, scrutiny of each individual research intervention and procedure in the study would result in removing duplicative procedures and thereby minimize risks to participants.

Potential individual benefits. Research has a range of potential individual benefits. It generates the knowledge necessary to protect and promote the health of future patients (the social and scientific value of research; see Guideline 1 – Scientific and social value and respect for rights). 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 potential individual benefit. Researchers, sponsors and research ethics committees must maximize the potential individual benefits of studies for both future patients and study participants. For instance, the social and scientific value of studies can be maximized by making data or specimens available for future research (see Guideline 24 – Public accountability for health-related research). 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 individual benefits need to be carefully balanced with competing considerations. For example, sharing data or specimens for future research can pose risks to participants, especially when adequate safeguards to protect confidentiality are not 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:

- ▶ monitoring the study and providing mechanisms for responding to adverse events;
- ▶ establishing a Data Safety and Monitoring Committee (DSMC) to review and decide on data on harms and benefits as a study progresses;
- ▶ instituting clear criteria for stopping a study;
- ▶ installing safeguards to protect the confidentiality of sensitive personal data;
- ▶ seeking exemptions, where possible, from requirements to report information about illegal activities of study participants (such as sex work in countries where prostitution is forbidden by law);
- ▶ avoiding unnecessary procedures (for example, by performing laboratory tests on existing blood samples instead of drawing new blood, where scientifically appropriate); and
- ▶ 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 scientific and 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 and the social and scientific value of the research. For interventions that have a prospect of potential individual benefit, risks are acceptable if they are outweighed by the potential individual 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 – Choice of control in clinical trials.

Judgments about the risk-benefit profile of study interventions, and how they compare with 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 and other documents submitted to the research ethics committee, a comprehensive and balanced overview of the available evidence that is relevant for evaluating the risks and potential individual 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 of the study intervention involving humans. They must also note in the documents sent to the committee any limitations of the available data as well as any disagreement about the foreseeable risks and potential individual benefits, including potential conflicts of interests that might influence conflicting opinions. Researchers should provide a credible interpretation of the available evidence to support their judgment that an investigational agent has a favourable risk-benefit ratio, and that its risk-benefit profile is at least as advantageous as the risk-benefit profile of any established alternatives. It is important to note, however, that the risks and potential individual benefits of study interventions can be difficult to predict before larger clinical trials have been conducted. This means that sponsors, researchers and research ethics committees may need to judge the risk-benefit profile of such interventions under conditions of considerable uncertainty.

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 unacceptable in relation to the social and scientific 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 individual benefits of the given study.

The minimal-risk standard. The minimal-risk standard is often defined by comparing the probability and magnitude of anticipated harms with the probability and magnitude of harms ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The purpose 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 relatively 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 risks 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. 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 study they are reviewing.

Risks to groups. In order to achieve the social and scientific value of research, results must be made public (see Guideline 24 – Public accountability for health-related research). However, research results in certain fields (for example, epidemiology, genetics, and sociology) may present risks to the interests of communities, societies, families, 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. Research results could therefore stigmatize a group or expose its members to discrimination. Plans to conduct such research should be sensitive to these considerations and minimize risks to groups, notably by maintaining confidentiality during and after the study and publishing the resulting data in a manner that is respectful of the interests of all concerned.

Similarly, conducting research may disrupt or interfere with providing health care to the local community and thereby pose risks to the community. Research ethics committees must ensure, as part of evaluating the risks and potential individual benefits of research studies, that the interests of all who may be affected are given due consideration. For example, researchers and sponsors could contribute to the local health infrastructure in a way that compensates for any disruption caused by the research.

In assessing the risks and potential individual benefits that a study presents to a population, research ethics committees should consider the potential harm that could result from forgoing the research or from failing to publish the results.

Risks to researchers. In addition to participants, investigators themselves can be exposed to risks that result from research activities. For example, research involving radiation can expose researchers to risks and studies on infectious disease can pose risks to laboratory staff who are handling samples. Sponsors should carefully assess and minimize risks to researchers; specify and explain the risks of undertaking the research to investigators and other research staff; and provide adequate compensation in case any members of the research team incur harm as a result of the research.

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 should be evaluated according to the criteria set out in Guideline 4 – Potential individual benefits and risks of research.

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 persons 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 factors.

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 accurate scientific information without delaying or withholding established effective interventions from participants. Researchers and sponsors may deviate from this rule when withholding such interventions is methodologically necessary and exposes participants to no more than a minor increase above minimal risk.

Although conventional randomized controlled clinical trials are often considered the gold standard, other study designs such as response-adaptive trial designs, observational studies, or historical comparisons 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 favourable when compared to a conventional randomized controlled trial.

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, especially 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. Trials may also be useful when the risk-benefit profile of a treatment is not clearly favourable, such that patients might reasonably forgo the usual intervention for the condition (for example, antibiotic treatment for otitis media in children, or arthroscopic knee surgery). When there are several treatment options 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 for specific groups. This may include testing an established effective intervention against a placebo, provided the conditions of this Guideline are met.

Some people contend that it is never acceptable for researchers to withhold or withdraw established effective interventions. Others argue that it may be acceptable, provided that the risks of withholding an established intervention are acceptable, and withholding the established effective intervention is necessary to ensure that the results are interpretable and valid. In such cases, an intervention known to be inferior, a placebo (see below) or no intervention may be substituted for the established intervention. This Guideline takes a middle stance on this issue. The preferred option is to test potential new interventions against an established effective intervention. When researchers propose to deviate from this option, they must provide a compelling methodological justification and evidence that the risks from withholding or delaying the established intervention are no greater than a minor increase above minimal risk.

These principles on the use of placebo also apply to the use of control groups who receive no treatment or who receive a treatment that is known to be inferior to an established treatment. Sponsors, researchers, and research ethics committees should evaluate the risks of providing no treatment (and no placebo) or an inferior treatment, compared to the risks and potential individual benefits of providing an established treatment, and apply the criteria for placebo use in this Guideline. In sum, when an established effective intervention exists, it may be withheld or substituted with an inferior intervention only if there are compelling scientific reasons for doing so; the risks of withholding the established intervention or substituting it with an inferior one will result in no more than a minor increase above minimal risk to participants; and the risks to participants are minimized.

Placebo. An inert substance or sham procedure is provided to research participants with the aim of making it impossible for them, and usually the researchers themselves, to know who is receiving an active or inactive intervention. Placebo interventions are methodological tools used with the goal of isolating the clinical effects of the investigational drug or intervention. This enables researchers to treat participants in the study arm and the control arm in exactly the same way, except that the

study group receives an active substance and the control group does not. The risks of the placebo intervention itself are typically very low or non-existent (for example, ingestion of an inert substance).

In some fields, such as surgery and anaesthesia, testing the effectiveness of interventions may require the use of sham interventions. For example, the participants in the active arm of a surgery trial may receive arthroscopic surgery on their knees, while participants in the control group may receive only a minor skin incision. In other cases, both groups may receive an invasive procedure, such as inserting a catheter into a person's artery. The catheter is threaded into the heart of participants in the active arm, but stopped short of the heart in participants in the control arm. The risks of sham procedures can be considerable (for example, surgical incision under general anaesthesia) and must be carefully considered by a research ethics committee.

Placebo controls. The use of placebo is usually 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 does not preclude comparing the effects of potential new interventions against a placebo control in cases where all participants receive the established effective intervention and are then randomized to the investigational intervention or placebo. Such add-on designs are common in oncology where all participants receive an established effective treatment, and are then randomized to placebo or the investigational intervention.

Alternatively, when there is credible uncertainty about the superiority of an established effective intervention over an investigational agent (“this is known as clinical equipoise”), it is permissible to compare its effects directly against an established effective intervention. In 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.

Finally, the use of placebo is usually uncontroversial when an established effective intervention is not known to be safe and effective in a particular local context. For example, viruses often have different strains whose occurrence varies geographically. An established vaccine may have been shown to be safe and effective against a particular strain, but there may be credible uncertainty about its effects against a different strain in a different geographical context. In this situation, it can be acceptable to use a placebo control because it is uncertain whether the established vaccine is effective in the local context.

Compelling scientific reasons. Compelling scientific reasons for placebo controls exist when a trial cannot distinguish effective from ineffective interventions without a placebo control (sometimes referred to as “assay sensitivity”). Examples of “compelling scientific reasons” include the following: the clinical response to the established effective intervention is highly variable; the symptoms of the condition fluctuate and there is a high rate of spontaneous remission; or the condition under study is known to have a high response to placebos. 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.

In some cases an established effective intervention is available but the existing data may have been obtained under conditions that are substantially different from local health care practices (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 – Research conducted in low-resource settings, and all other requirements in these Guidelines are met.

When a researcher invokes compelling scientific reasons to justify the use of placebo, the research ethics committee should seek expert advice, if such expertise is not already present among members of the committee, 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 by one of the conditions in this Guideline, the possibly harmful effects of receiving this comparator must be minimized consistent with the general requirements to minimize the risks of research interventions (Guideline 4 – Potential individual benefits and risks of research). The following conditions apply to placebo-controlled trials.

First, researchers must decrease the period of placebo use to the shortest possible time 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”). The protocol should establish a threshold beyond which the participant should be offered the active treatment.

Second, as discussed in Guideline 4 – Commentary, the researcher must minimize harmful effects of placebo-controlled studies by providing safety monitoring of research data during the trial.

Minimal risks of receiving placebo. Risks of receiving placebo count as minimal when the risk of serious harm is very unlikely and the potential harms associated with more common adverse events are small, as described in Guideline 4 – Potential individual benefits and risks of research. For example, when the investigational 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 groups 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 – Potential individual benefits and risks of research, the minor increase above minimal risk standard also applies to placebo-controlled trials.

Placebo control in a low-resource setting when an 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 possible to implement or made 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). This can involve testing 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. Considerable controversy exists in this situation regarding which trial design is both ethically acceptable and necessary to address the research question. Some argue that such studies should be conducted with a non-inferiority design that compares the study intervention with an established effective method. Others argue that a superiority design using a placebo can be acceptable.

The use of placebo controls in these situations is ethically controversial for several reasons:

1. Researchers and sponsors knowingly withhold an established effective intervention from participants in the control arm. However, when researchers and sponsors are in a position to provide an intervention that would prevent or treat a serious disease, it is difficult to see why they are under no obligation to provide it. 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 in low-resource settings in order to develop affordable 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 increased funding from international agencies should be sought.

When controversial, placebo-controlled trials are planned, 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 or priorities of the host country (see Guideline 2 – Research conducted in low-resource settings); and
2. ascertain whether arrangements have been made for the transition to care after research for study participants (see Guideline 6 – Caring for participants' health needs), including post-trial arrangements for implementing any positive trial results, taking into consideration the regulatory and health care policy framework in the country.

Comparative effectiveness and 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, as well as systematic reviews, have received growing attention over the past few years. In comparative effectiveness research, two or more interventions regarded as standards of care are directly compared. Comparative effectiveness research may help to determine which standard of care has better outcomes or more acceptable risks. Research ethics committees should carefully distinguish between marketing studies that aim to position a product (sometimes called seeding trials) and comparative effectiveness studies in which scientific and public health perspectives are the primary objectives. Research ethics committees should not approve the first type of studies.

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 example 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 potential individual benefit or the social value of the research (see Guideline 4 – Potential individual benefits and risks of research).

GUIDELINE 6:

CARING FOR PARTICIPANTS' HEALTH NEEDS

Especially in the context of clinical trials, researchers and sponsors must make adequate provisions for addressing participants' health needs during research and, if necessary, 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 assistance and established effective care is available locally.

When participants' health needs during and after research cannot be met by the local health infrastructure or the participant's pre-existing health insurance, the researcher and sponsor must make prior arrangements for adequate care for participants with local health authorities, members of the communities from which persons are drawn, or nongovernmental organizations such as health advocacy groups.

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

- ▶ how care will be adequately provided for the condition under study;
- ▶ how care will be provided during the research when researchers discover conditions other than those under study ("ancillary care");
- ▶ transitioning participants who continue to need care or preventive measures after the research to appropriate health services;
- ▶ providing continued access to study interventions that have demonstrated significant benefit; and
- ▶ consulting with other relevant stakeholders, if any, to determine everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has demonstrated significant benefit in the study.

When access is provided after the research to investigational interventions that have demonstrated significant benefit, the provision may end as soon as the study intervention is made available through the local public health-care system or after a predetermined period of time that the sponsors, researchers and community members have agreed before the start of a trial.

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

Commentary on Guideline 6

General considerations. It is generally inappropriate to require researchers or sponsors to take on the role of a country's health systems. Nevertheless, research with humans often involves interactions that enable researchers to detect or diagnose health problems during recruitment and the conduct of research. Similarly, clinical research often involves care and preventive measures in addition to the 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 demonstrated significant benefit. In all these situations, researchers and sponsors must show care and concern for the health and welfare of study participants. This is justified by the principle of beneficence, which requires researchers and sponsors to safeguard the health of participants when it is in their power to do so. It is also supported by the principle of reciprocity; participants assist researchers in generating valuable data and, in return, researchers should ensure that participants receive needed care or preventive measures 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 – Research conducted in low-resource settings) but is a universal ethical requirement in research. Furthermore, even though the provision of care during and after the trial may be an incentive for people in low-resource settings to enrol, it should not be considered an undue influence.

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. Nevertheless, when prospective participants cannot be enrolled in a study because they do not meet the inclusion criteria, or enrolled participants are found to have diseases unrelated to the research, researchers should advise them to obtain or refer them for medical care. In some circumstances, it may be relatively easy for researchers to treat the condition or refer participants to a centre 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. How to provide 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 in the host country. Accordingly, before research begins agreement must be reached on how to provide care to participants who already have, or who develop, diseases or conditions other than those being studied (for example, whether care will be provided for health conditions that are readily treated in the local health-care system).

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 health care after the research has ended. At a minimum, researchers must link participants in need of continued medical attention to an appropriate health service at the end of their participation in the study and communicate relevant information to the health service. The researchers themselves might continue to provide follow-up for a certain period of time, possibly for research purposes, and then transfer care to an appropriate provider. The obligation to provide transition to care following the research applies to both participants in the control arm and the intervention arm.

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 demonstrated significant benefit in the study or to established effective interventions that were provided as part of the standard of care or prevention to all participants during the research. Access should also be provided, when pertinent, in the interval between the end of the individual's participation and the end of the study. In this situation, access could be arranged by an extension study or by compassionate use. This obligation depends on several factors. For example, if discontinuing an intervention will deprive participants of basic capabilities, such as the ability to

communicate or function independently, or significantly reduce a quality of life they had attained during the study, then the obligation will be greater than if the intervention provides relief for a minor or transient condition. Similarly, the obligation will be greater when 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 when there are no available alternatives with clinical effectiveness similar to the intervention that has demonstrated significant benefit than in cases where such alternatives exist. However, the obligation may not be able to be completely met if the total number of qualifying individuals is very large. Continued access to interventions that have demonstrated significant benefit but await regulatory approval should be consistent with the relevant regulatory requirements for pre-licensure access and should not delay the process of obtaining regulatory approval.

Providing continued access to a beneficial study intervention can create several dilemmas:

- ▶ In the case of blinded controlled trials, it may take time to unblind the results and find out who has received which intervention. Researchers and sponsors should make provisions for this transition period and inform participants if they will be temporarily receiving the current standard of care before the study 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.

As stated in this Guideline, sponsors and researchers may no longer have an obligation to provide continued access to a study intervention that has demonstrated significant benefit when the intervention becomes available in the public health system. Moreover, sponsors, researchers and community members may agree before a trial starts that any intervention that has demonstrated significant benefit will be provided only for a predetermined period of time.

Consultation with relevant stakeholders. The obligation to care for participants' health needs rests with the researcher and the sponsor. However, the delivery of care may involve other parties, for example, local health authorities, insurance companies, members of the communities from which participants are drawn, or nongovernmental 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 have agreed to the plan. Research ethics committees must determine whether the arrangements for continued care are adequate.

Decisions on how to fulfil the obligation to provide transition to care are best made for each study through a transparent and participatory process that involves all relevant stakeholders before the study begins (see Guideline 7 – Community engagement). This process must explore options and determine the core obligations in the particular situation with regard to the level, scope, and duration of any post-trial care and treatment package; equitable access to services; and the responsibility for provision of services. 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. When participants are informed about the extent of ancillary care, if any, to be provided, this information should be clearly separated from information about the study interventions and research procedures.

Access to study interventions for communities. Obligations to provide beneficial post-trial interventions to communities are discussed in Guideline 2 – Research conducted in low-resource settings.

GUIDELINE 7:

COMMUNITY ENGAGEMENT

Researchers, sponsors, health authorities 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, design of the informed consent process and monitoring of research, and in the dissemination of its results.

Commentary on Guideline 7

General considerations. Proactive and sustained engagement with the communities from which participants will be invited to participate is a way of showing respect for them and the traditions and norms that they share. Community engagement is also valuable for the contribution it can make to the successful conduct of 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 social value and outcome of proposed research. Community engagement 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.

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. Stakeholders are individuals, groups, organizations, government bodies, or any others who can influence or are affected by the conduct or outcome of the research project. 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, regulatory authorities, government agencies and community advisory boards. Also, it is important to ensure diversity of views within the consultation process. For instance, when community leaders are men only, researchers should actively include the views of women, as well. There may also be value in consulting individuals who have previously participated in comparable studies.

The research protocol or other documents submitted to the research ethics committee should include a description of the plan for community engagement, and identify resources allocated for the proposed activities. This documentation must specify what has been and will be done, when and by whom, to ensure that the community is clearly defined and can be proactively engaged throughout the research to ensure that it is relevant to the community and is accepted. The community should participate, when feasible, in the actual discussion and preparation of the research protocol and documents.

Researchers, sponsors, health authorities and relevant institutions should take care that community engagement does not lead to pressure or undue influence on individual community members to participate (see commentary on Guideline 9 – Individuals capable of giving informed consent, section

on *Dependent relationship*). In order to avoid such pressure, individual informed consent must always be sought by the researcher.

Researchers and research ethics committees should be cognizant of the point at which the process of community engagement becomes a stage of formative research that itself requires ethics review. Examples of community engagement processes that may require ethics review include systematic data collection that can be generalized and disseminated in forums outside of the community in which they were implemented, as well as any data generation that could create social risks for participants.

Engagement at the earliest opportunity. Before a study is initiated, the community from which participants will be recruited should, when feasible, be consulted about their research priorities, preferred trial designs, willingness to be involved in the preparation 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 should be encouraged to 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.

Community engagement should be an ongoing process, with an established forum for communication between researchers and community members. This forum 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 with community members is a mutually educative process, which both enables researchers to learn about communities' cultures and understanding of research-related concepts, and contributes to research literacy by educating the community about key concepts critical for understanding the purpose and procedures of the research. Good-quality community engagement helps to ensure that existing community dynamics and power inequities are not allowed to derail the process of ensuring the comprehensive engagement of all relevant community stakeholders. Care should be taken to solicit the views of all sectors of the community proactively and sensitively. Community members should be invited to 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, site selection, data collection and sharing, ancillary care and post-trial availability of any developed interventions for populations and communities (see Guideline 2 – Research conducted in low-resource settings, and Guideline 6 – Caring for participants' health needs). 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 in advance who will have the final say. The community must not be permitted to insist on including or omitting certain procedures that could threaten the scientific validity of the research. At the same time, 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 unable to be resolved, the research may have to be forgone (see Guideline 8 – Collaborative partnership and capacity-building for research and research review). If a research ethics committee is confronted with a severe split in the community about the design or conduct of a proposed study, the committee should urge the researchers to conduct the study in another community.

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 should engage with these initiatives, which can offer valuable insights into their own work.

GUIDELINE 8:

COLLABORATIVE PARTNERSHIP AND CAPACITY-BUILDING FOR RESEARCH AND RESEARCH REVIEW

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. Independent scientific and ethical review is critical to engender community trust for research (see Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols). Health-related research often requires international collaboration and 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 should contribute to capacity-building for research and review.

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

- ▶ research infrastructure building and strengthening research capacity;
- ▶ strengthening research ethics review and oversight capacity in host communities (see Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols);
- ▶ 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 participants will be drawn (see Guideline 7 – Community engagement);
- ▶ arranging for joint publication consistent with recognized authorship requirements and data sharing (see Guideline 24 – Public accountability for health-related research); and
- ▶ preparing a benefit-sharing agreement to distribute eventual economic gains from the research.

Commentary on Guideline 8

General considerations. Governmental authorities in charge of health-related research involving human participants have to ensure that such research is reviewed ethically and scientifically by competent and independent research ethics committees and is conducted by competent research teams (see Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols). 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 ethical review. Before undertaking research in a community with little or no such capacities, sponsors and researchers should have a plan that describes how the research can contribute to local capacity. The kind and amount of capacity-building reasonably required should be proportional to the magnitude of the research project. A brief epidemiological study involving only review of medical records, for example, would require 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 require international cooperative research. Real or perceived disparities in power or expertise should be resolved in a way that ensures equity 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 North-South cooperation that sustains site research capacity. To safeguard against power differences, innovative forms of collaboration should be considered. For example, the following three steps may promote inclusion, mutual learning and social justice. At the start of a collaboration and before even beginning a specific research project: i) determine the local research agenda; ii) determine capacity needs or priorities assessment amongst partners of international health research; and iii) create a Memorandum of Understanding (MoU).

Collaborative partnership also helps to ensure the social value of research by engaging the communities, thereby focusing on research the community considers valuable (see Guideline 1 – Scientific and social value and respect for rights, and Guideline 7 – Community engagement).

Strengthening research capacity. The specific capacity-building objectives should be determined and achieved through dialogue and negotiation among the sponsor, researchers and other relevant stakeholders, such as community boards and host-country authorities. These stakeholders should agree on joint efforts to strengthen research capacity as a component of the country's health system, and optimize its sustainability for further generation of new knowledge. Local principal investigators should be involved in the research project.

Capacity-building and conflicts of interest. Capacity-building may give rise to conflicts of interests. The following interests may conflict: the desire of the sponsor to conduct the research; the wishes of potential participants regarding their enrolment; the desire of investigators to access the latest medications for their patients and contribute to knowledge; and the commitment of local community leaders to compensate for inadequate research funding by bringing in sponsored research to build their infrastructure. Research ethics committees should evaluate whether capacity-building efforts may involve such conflicts of interests and seek ways to mitigate them (see Guideline 25 – Conflicts of interest).

Strengthening ethical review. Researchers and sponsors who plan to perform research in settings where research ethics committees are absent or lack adequate training should help to establish such committees, to the extent reasonably possible, 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 from researchers and sponsors must not be provided directly and must never be tied to the committee's decision about specific protocols (see Guideline 25 – Conflicts of interest). Rather, funds must be made available specifically for research ethics capacity-building. 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. Collaborative research should lead to jointly (external and in-country) authored, open-access publications (see Guideline 24 – Public accountability for health-related research). Researchers and sponsors must provide fair opportunities to enable joint authorship consistent with recognized authorship requirements, such as those of the International Committee of Medical Journal Editors (ICMJE).

GUIDELINE 9:

INDIVIDUALS CAPABLE OF GIVING INFORMED CONSENT

Researchers have a duty to provide potential research participants with the information and the opportunity to give their free and informed consent to participate in research, or to decline to do so, unless a research ethics committee has approved a waiver or modification of informed consent (see Guideline 10 – Modifications and waivers of informed consent). Informed consent should be understood as a process, and participants have a right to withdraw at any point in the study without retribution.

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;
- ▶ refrain from unjustified deception or withholding of relevant information, undue influence, or coercion (see Guideline 10 – Modifications and waivers of informed consent);
- ▶ ensure that the potential participant has been given sufficient opportunity and time 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 seek the approval of the research ethics committee.

With 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. In long-term studies, researchers should ensure at pre-determined intervals that each participant is willing to stay in the study, even if there are no changes in the design or objectives of the research.

It is the principal investigator's responsibility 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 individuals capable of giving informed consent 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 plain 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. Participants should be offered the opportunity to ask questions and receive answers before or during the research. Researchers should make every effort to address those questions in a timely and comprehensive manner.

This Guideline applies to individuals capable of giving informed consent. Requirements for research with individuals who are not capable of giving informed consent or with children and adolescents are set out in Guideline 16 – Research involving adults incapable of giving informed consent, and Guideline 17 – Research involving children and adolescents.

Process. Informed consent is a two-way communicative process that begins when initial contact is made with a potential participant and ends when consent is provided and documented, but can be revisited later during the conduct 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.

Language of the information leaflet and recruitment material. All potential participants should be provided with a written information leaflet that they may take with them. Informing the individual participant must not be simply a ritual recitation of the contents of a written document. The wording of the leaflet and any recruitment material must be in language understandable by the potential participant and be approved by the research ethics committee. The wording of the leaflet must be short and preferably not exceed two or three pages. An oral presentation of information or the use of appropriate audiovisual aids, including pictographs and summary tables, are important to supplement written information documents to aid understanding. Information should also be appropriate for the participant group and specific individual, for example, in braille. Informed consent shall not include any language through which the subject is made to waive or appear to waive any of the participant's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Contents of the information leaflet. Throughout these Guidelines, elements that need to be included in the information leaflet are specified. Appendix 2 contains the details of information that must be provided, as well as possible supplementary information. This list mentions, but is not limited to, information about the aims, methods, sources of funding, possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-trial access and any other relevant aspects of the study.

Comprehension. The person obtaining consent must ensure that the potential participant has adequately understood the information provided. Researchers should use evidence-based methods for imparting information to ensure comprehension. The potential participant's ability to understand the information depends, among other things, on the 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.

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 should sign a consent form, or, where the individual lacks decisional capacity, a legal guardian or other duly authorized

representative must do so (see Guideline 16 – Research involving individuals incapable of giving informed consent, and Guideline 17 – Research involving children and adolescents). The research ethics committee may approve a waiver of the requirement of a signed consent document under certain conditions (see Guideline 10 – 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 behaviour. In some cases, especially when the information is complicated, participants should be given information sheets to retain; these may resemble conventional sheets 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 should provide to the research ethics committee documentation of consent, certified either by the person obtaining consent or by a witness at the time consent is obtained.

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 a school or a prison, or from a community leader, a council of elders, or another designated authority. Such institutional procedures or cultural customs should 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 use culturally appropriate ways to communicate information necessary for adherence to the requirements of the informed consent process. They must also describe and justify in the research protocol the procedure they plan to use in communicating information to participants. 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 an individual's decision to participate is free from undue influence. A variety of factors may affect the voluntariness with which consent is provided. Some of these factors 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 being undue, and if so, 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 assumes the role of researcher. The dependent relationship between patients and clinician-researchers may compromise the voluntariness of informed consent, since potential participants who are patients depend on the clinician-researcher for medical care and may be reluctant to refuse an invitation to enrol in research in which the treating clinician is involved. Therefore, in principle, in the case of a dependent relationship a neutral third party such as a research nurse or a qualified collaborator,

should obtain informed consent. However, in some situations of dependency, it is preferable that the clinician provide the patient with information since he or 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. Clinicians engaged in research must acknowledge and inform patients that they have a dual role as the treating clinician and researcher. They must emphasize the voluntary nature of participation and the right to refuse or withdraw from the research. They must also assure patients that their decision whether to enrol or 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.

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

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, for instance in the case of a dependent relationship, is permissible as long as the person who obtains consent is duly qualified and has prior experience in obtaining consent. The principal investigator is responsible for ensuring that all personnel working on the project comply with this Guideline.

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 – Modifications and waivers of informed consent - are met. When a researcher plans 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 (see Guideline 12 – Collection, storage and use of data in health-related research). If researchers wish 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. Before a waiver of informed consent is granted, researchers and research ethics committees should 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;**
- ▶ **the research has important social value; and**
- ▶ **the research poses no more than minimal risks to participants.**

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 providing information and documenting the participant's informed consent. A waiver of consent allows researchers to conduct studies without obtaining fully informed consent.

As stated in Guideline 9 – Individuals capable of giving informed consent, individuals or their legally authorized representatives must give their 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 make a meaningfully informed decision whether or not to participate. For instance, in some cases it may be possible to describe the purpose of a study without informing potential participants of the detailed procedures in the trial arms.

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 health-related 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, potential participants must be asked to consent to remain uninformed of the purpose of some procedures until the research is completed. After their participation in the study ends, they must 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 have been collected. Any such procedure may be implemented only if it receives explicit approval from a research ethics committee. Moreover, before study results are analysed, participants must be provided with the information withheld and given the possibility to withdraw their data collected under the study. The potential impact on the validity of the study when participants withdraw their data must be considered before a study starts.

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 behavioural scientists sometimes deliberately misinform participants in order to study their attitudes and behaviour. For example, researchers use “pseudo-patients” or “mystery clients” to study the behaviour 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 the study exposes participants to more than minimal risk. When deception is deemed indispensable for obtaining valid results in 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 pretences. 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 (meaning that researchers obtain consent in advance for the deception). The research ethics committee must determine how 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 data 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, studies involving “mystery” clients or patients).

Waiving informed consent. A research ethics committee may waive informed consent if it is convinced that the research would not be feasible or practicable to carry out without the waiver, 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 identifiable data or biological specimens, meaning that the data or specimens carry a person’s name or are linked to a person by a code. The conditions must also be met when studies analyse existing data from health-related registries, and when the participants are children, adolescents, and individuals not capable of giving informed consent (Guideline 16 – Research involving adults incapable of giving informed consent, and Guideline 17 – Research involving children and adolescents).

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 participants 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 using data in health-registries. The creation and maintenance of health-related registries (for example, cancer registries and databanks of genetic and other anomalies in newborn babies) provide a major resource for many public health and epidemiological research activities, 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 established as mandatory by governmental authorities usually involve obligatory rather than voluntary collection of data.

When a 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. At the same time, consent cannot be waived when public health authorities conduct studies in which data in the registries are combined with new activities that involve direct contact with persons, such as studies in which they obtain information from individuals by using questionnaires. 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 involving internal institutional activity of a registry.

GUIDELINE 11:

COLLECTION, STORAGE AND USE OF BIOLOGICAL MATERIALS AND RELATED DATA

When biological materials and related data, such as health or employment records, are collected and stored, institutions must have a governance system to obtain authorization for future use of these materials in research. Researchers must not adversely affect the rights and welfare of individuals from whom the materials were collected.

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 person from whom the material originally is obtained. The ethical acceptability of broad informed consent relies on proper governance. This type of consent must be obtained in the same way as described in Guideline 9 – Individuals capable of giving informed consent.

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 must fulfil 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 the requirement of individual informed consent if: 1) the research would not be feasible or practicable to carry out without the waiver; 2) the research has important social value; and 3) the research poses no more than minimal risks to participants or to the group to which the participant belongs.

Custodians of biological materials must arrange to protect the confidentiality of the information linked to the material, by sharing only anonymized or coded data with researchers, and limiting access to the material of third parties. The key to the code must remain with the custodian of the biological material.

The transfer of biological materials must be covered by a Material Transfer Agreement (MTA).

Biological materials and related data should only be collected and stored in collaboration with local health authorities. The governance structure of such collection should have representation of the original setting. If the specimen and data are stored outside the

original setting, there should be provisions to return all materials to that setting and share possible results and benefits (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research, Guideline 7 – Community engagement, and Guideline 8 – Collaborative partnership and capacity building for research and review).

Commentary on Guideline 11

General considerations. Research involving human biological materials may include: tissues, organs, blood, plasma, skin, serum, DNA, RNA, proteins, cells, hair, nail clippings, urine, saliva, or other bodily fluids. These biological materials may come from a variety of places but the materials will mostly come from patients following diagnostic or therapeutic procedures, autopsy specimens, and donations of organs or tissue from living or dead humans, or bodily wastes or abandoned tissue. They may be collected expressly for a specific research purpose; from medical or diagnostic procedures with no initial intent to be used in research; or for research or medical or diagnostic purposes with the expectation that they may, or will, also be used in future research, although the precise research project(s) may not be known at the time. The value of bio-repositories for longitudinal studies of specific diseases is widely recognized. For this purpose, population biobanks have been established to allow studies across many diseases through correlations of genetic, environmental, occupational, and other health data.

In this Guideline, the term biobank is used for the collection of stored biological materials and associated data. The term biobank may refer to both large population biobanks and small bio-repositories consisting of bio-specimens in laboratories.

An individual whose biological materials and related data are used in research is a study participant and ethical guidelines that apply to research participants are applicable in this situation. This *mutatis mutandis* should also apply in cases where the research uses samples and data from deceased individuals. The vast majority of people do not object to their materials and related data being stored in repositories and used for research for the common good. However, the person whose materials are stored (the donor) must, in principle, explicitly authorize future use by one of the mechanisms described in this Guideline. Since the precise nature of the research is typically unknown, it is impossible to obtain specific informed consent at the time the material is collected. Therefore, broad informed consent for future use is an acceptable alternative to specific informed consent. Broad informed consent requires 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-overs” from clinical diagnosis or treatment 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 material is controlled;
- ▶ 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 what circumstances;
- ▶ which body may review research proposals for future use of the material;
- ▶ appropriate mechanisms for keeping donors informed of research outcomes;
- ▶ 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 excluded or included only after recontacting the donor for consent;
- ▶ to whom any benefits from the research are expected to accrue;
- ▶ appropriate mechanisms for keeping participants informed of research outcomes; and
- ▶ how the rights and welfare of individuals from whom the materials were collected are not adversely affected.

All governance systems should follow the principle of accountability and should maintain good stewardship of stored biological materials and related data. None of the regulations concerning the storage, use and final fate of biological samples should contradict or overrule conditions originally stated in (broad) informed consent documents and agreed to by research participants.

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 specifically agreed to by the donor, if the donor has given 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 the requirement of individual informed consent for research with historical materials provided the above three conditions mentioned in the bold text of this Guideline are met (see Guideline 10 – Modifications and waivers of informed consent).

Specific informed consent. When the future use of the materials is known at the time of collection, specific informed consent must be obtained as described in Guideline 9, Individuals capable of giving informed consent. Persons who were incapable of giving informed consent at the time their bodily material was stored must be given the opportunity to give informed consent or refusal if researchers know, or reasonably should have known that the subject has become capable of giving informed consent (see also Guideline 16 – Research involving adults incapable of giving informed consent).

Broad informed consent. Broad informed consent encompasses the range of future uses in research for which consent is given. Broad informed consent is not blanket consent that would allow future use of bodily material without any restriction. On the contrary, broad informed consent places certain limitations on the future use of bodily materials. Broad informed consent forms should specify: the purpose of the biobank; the conditions and duration of storage; the rules of access to the biobank; the ways in which the donor can contact the biobank custodian and remain informed about future use; 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; the intended goal of such use, whether only for basic or applied research, 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, following this practice in every situation in health care may be overly demanding and difficult to implement; therefore, an informed opt-out procedure may be acceptable. This implies 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 fulfil 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.

An informed opt-out procedure for research on residual tissue may not be appropriate in certain circumstances, namely a) when the research involves more than minimal risks to the individual, 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 certain tissue types, for example gametes, or d) when research is conducted in contexts of heightened vulnerability. A research ethics committee must determine whether explicit informed consent for the research is required.

Withdrawal of consent. Donors or their legal representatives should be able to withdraw consent for maintenance and use of biological material stored in a biobank. The withdrawal of consent should be formalized by written documentation signed by the donor or their legal representative of the donor, and the samples should either be destroyed or returned to the donor. Future use of the biological materials and related data is not permitted after the withdrawal of consent.

Authorization for research with archived materials. When biological materials and data collected and stored in the past without specific or broad informed consent contain important and otherwise unobtainable data, a research ethics committee needs to decide whether the use of such materials is justified. 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. For example, this may happen when the study involves review of hospital records or performing new tests on blood 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 or to the group from which the participant originates.

Confidentiality. An important aspect of storing human biological material is confidentiality guaranteed to the donor. The information resulting from analysis of the material could, if disclosed to third parties, cause harm, stigma or distress. Those responsible for biobanks must arrange to protect the confidentiality of such information by, for example, providing only anonymized or coded data to researchers and limiting access of the material of third parties. During the process of obtaining informed consent, those responsible for the biobank must inform the potential donors about the safeguards that will be taken to protect confidentiality as well as their limitations. Biological material stored in biobanks must be anonymized or coded. When researchers use coded materials obtained from biobanks in later studies, the key to the code must remain with the custodian of the biobank. Thus researchers can use only anonymized or coded material. It should be acknowledged that the possibility of complete anonymization is becoming increasingly illusory as the possibility of cross-matching large datasets improves. The more difficult it becomes to anonymize data, the more important it will be to retain the ability to remove personal data from a dataset. This is a crucial part of the governance system specified above.

Return of results and disclosure of (un)solicited findings. Generally, biobanks store coded material in order to be able to link this material to health data. This means that research findings,

whether unsolicited or not, can be returned to the donor. The informed consent process must clearly stipulate whether return of information derived from analysis of the materials is foreseen, if the donor wishes. The information given to the donor should clearly state that providing individual diagnoses is not the purpose of the biobank or future research project, in order to prevent that donors are falsely reassured by the absence of unsolicited findings.

There is an emerging consensus that at least some findings in genetic research must be returned to individual donors if they wish. Tiered consent, meaning the possibility of obtaining packages or subsets of information, gives donors a range of choices and allows them to choose some options to give them greater control over the use of their biological materials. In general, the three guiding principles for return of results need to be followed: results must have analytical validity, clinical significance and actionability to qualify for being returned. This implies that 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 clinical significance would not qualify for communication to the participant. The research ethics committee should also evaluate whether individual counselling is necessary when returning particular genetic findings. Some cases may require making an ethically responsible management plan for returning (un)solicited findings.

Children and adolescents. Children and adolescents who reach the age of maturity during the research project should be given the opportunity to give informed consent for the continued storage and use of their material and related data, and they should also be able to withdraw consent for future research. An informed, opt-out system in which such persons are alerted to their right to withdraw could also be acceptable.

Material Transfer Agreement. The transfer of human biological materials must be covered by a material transfer agreement (MTA). This MTA must ensure that the biological materials are documented in such a way that they can be retrieved. The range and duration of use and what needs to happen at the end of the period of use must also be specified. All responsibilities concerning these elements of an MTA need to be clearly stated in the agreement. An MTA is also needed in multinational research projects in which one entity collects samples from persons in all participating countries and stores them in a single biobank.

Closure of a biobank. In the event of closure of the biobank, plans for appropriate transfer or disposal of the biological material and data should be developed in collaboration with local health authorities.

Storing and using material from low-resource settings in biobanks. Biobanks have become a global phenomenon. Nevertheless, some low-resource settings may be inexperienced in storing and using biological materials. 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 Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research, Guideline 7 – Community engagement, and Guideline 8 – Collaborative partnership and capacity building for research and review).

GUIDELINE 12:

COLLECTION, STORAGE AND USE OF DATA IN HEALTH-RELATED RESEARCH

When data are stored, institutions must have a governance system to obtain authorization for future use of these data in research. Researchers must not adversely affect the rights and welfare of individuals from whom the data were collected.

When data are collected and stored for research purposes, either specific informed consent for a particular use or broad informed consent for unspecified future use must be obtained from the person from whom the data were originally obtained. The ethical acceptability of broad informed consent relies on proper governance. This type of informed consent must be obtained in the same way as described in Guideline 9 – Individuals capable of giving informed consent.

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. However, a person's objection is not applicable when it is mandatory to include data in population-based registries. The informed opt-out procedure must fulfil 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 having obtained informed consent for their future use for research, the research ethics committee may consider to waive the requirement of individual informed 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 or to the group to which the participant belongs.

Custodians of the data must arrange to protect the confidentiality of the information linked to the data, by sharing only anonymised or coded data with researchers, and limiting access to the material of third parties. The key to the code must remain with the custodian of the data.

Data from low-resource settings should only be collected and stored 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 should be provisions to return all data to that setting and share possible results and benefits (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research, Guideline 7 – Community engagement, and Guideline 8 – Collaborative partnership and capacity building for research and review).

Commentary on Guideline 12

General considerations. The value of data collections for longitudinal studies of specific diseases is widely recognized. Databanks may include all types of health-related data, including medical records, and patient health records. This Guideline is intended to cover health-related data beyond the individual care of patients.

As with biobanks, the vast majority of people do not object to their data being stored in collections and used for research for the common good. The person whose data are stored (the donor) must, in principle, explicitly authorize future use by one of the mechanisms described in this Guideline. Since the precise nature of the research is typically unknown, it is impossible to obtain specific informed consent at the time the data are collected. Therefore, broad informed consent for future use is an acceptable alternative to specific informed consent. Broad informed consent requires proper governance and management of the databank.

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 data 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 what circumstances;
- ▶ which body may review research proposals for future use of the data;
- ▶ appropriate mechanisms for keeping donors informed of research outcomes;
- ▶ 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 excluded or included only after recontacting the donor for consent;
- ▶ to whom any benefits from the research are expected to accrue;
- ▶ appropriate mechanisms for keeping participants informed of research outcomes; and
- ▶ how the rights and welfare of individuals from whom the data were collected are not adversely affected.

All governance systems should follow the principle of accountability and should maintain good stewardship of stored data. None of the regulations concerning the storage, use and final fate of health-related data should contradict or overrule conditions originally stated in (broad) informed consent documents and agreed to by research participants.

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 donor, if the donor has given 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 the requirement of individual informed consent for research with historical data provided the above three conditions mentioned in the bold text of this Guideline are met (see Guideline 10 – Modifications and waivers of informed consent). For population-based registries, internal institutional research activity of the registry may be exempted from review by a research ethics committee according to applicable law.

Specific informed consent. When the future 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 – Individuals capable of giving informed consent. Persons who were incapable of giving informed consent at the time their data were stored must be given the opportunity to give informed consent or refusal if researchers know, or reasonably should have known, that the subject has become capable of giving informed consent (see also Guideline 16 – Research involving adults incapable of giving informed consent).

Broad informed consent. Broad informed consent encompasses the range of future uses in research for which consent is given (see Guideline 11 – Collection, storage and use of biological materials and related data). Broad informed consent should specify: the purpose of the databank; the conditions and duration of storage; the rules of access to the databank, the ways in which the donor can contact the databank custodian and remain informed about future use; 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; 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; the intended goal of such use, whether only for basic or applied research, 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 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 are stored and used for research unless a person from whom the data originate explicitly objects. The informed opt-out procedure has to fulfil 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. However, in certain circumstances the researcher must obtain explicit informed consent, whether specific or broad: 1) when the research involves more than minimal risks to the individual; or 2) when controversial or high-impact techniques are used; or 3) when research is conducted in contexts of heightened vulnerability. A research ethics committee must determine whether explicit informed consent is required.

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.

Withdrawal of consent. Donors or their legal representatives at any time and without any charges or losses, should have the possibility to withdraw their consent for use of data in a databank. The withdrawal of consent should be formalized by written documentation signed by the donor or

the legal representative of the donor, and the data should be either destroyed or returned to the donor. Future use of the data is not permitted after the withdrawal of consent.

Authorization for research with archived data. When existing data, collected and stored without a specific or broad informed consent process, offer important and otherwise unobtainable information, a research ethics committee needs to decide whether the use of such data is justified. 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. In addition, the research must have important social value, and the research must pose no more than minimal risks to participants or to the group from which the participant originates.

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 wish 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 wish 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 – Individuals capable of giving informed consent).

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. Health-related data may contain a very large range of information. Therefore, an important aspect of storing health-related data is confidentiality. The collection and storage of information could, if disclosed to third parties, cause harm, stigma or distress. Those responsible for databanks must arrange to protect the confidentiality of such information by, for example, providing only anonymized or coded data to researchers and limiting access of the data to third parties. During the process of obtaining informed consent, those responsible for the databank must inform the potential donors about the safeguards that will be taken to protect confidentiality as well as their limitations. Data stored in databanks must be anonymized or coded. When researchers use coded materials obtained from databanks in later studies, the key to the code must remain with the custodian of the databank. Thus researchers can only use anonymized or coded material. It should be acknowledged that the possibility of complete anonymization is becoming increasingly illusory as the possibility of cross-matching large datasets improves. The more difficult it becomes to anonymize data, the more important it will be to retain the ability to remove personal data from a dataset. This is a crucial part of the governance system specified above.

When linked data 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. Donors must be informed of the 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 enable 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 – Individuals capable of giving informed consent). The more difficult it becomes to truly anonymize data, the more important it becomes for the participant to retain the ability to remove personal data from a dataset. Therefore, this is a crucial part of the governance system specified above.

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.

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 whether return of information derived from analysis of the data is foreseen, if the donor wishes. The information given to the donor should clearly state that providing individual diagnoses is not the purpose of the databank or future research project, in order to prevent that donors being falsely reassured by the absence of unsolicited findings.

There is an emerging consensus that at least some findings in genetic research must be returned to individual donors if they wish. Tiered consent, meaning the possibility of obtaining packages or subsets of information, gives donors a range of choices and allows them to choose some options to give them greater control over the use of their data. In general, the three guiding principles for return of results need to be followed: results must have analytical validity, clinical significance and actionability to qualify for being returned. This implies that 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 clinical significance would not qualify for communication to the donor. The research ethics committee should also evaluate whether individual counselling is necessary when returning particular genetic findings. Some cases may require making an ethically responsible management plan for returning (un)solicited findings.

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 – Public accountability for health-related research.

Children and adolescents. Children and adolescents who reach the age of maturity must be given the opportunity to give broad informed consent for the continued storage and use of their data and should also be able to withdraw consent for future research. An informed, opt-out system in which such persons are alerted to their right to withdraw, could also be acceptable.

Closure of a databank. In the event of closure of the databank, plans for appropriate transfer or disposal of the health-related data should be developed in collaboration with local health authorities.

Storing and using data from low-resource settings in databanks. Databanks have become a global phenomenon. Nevertheless, some low-resource settings may be inexperienced in storing and using biological materials. 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 Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research, Guideline 7 – Community engagement, and Guideline 8 – Collaborative partnership and capacity building for research and review).

GUIDELINE 13:

REIMBURSEMENT AND COMPENSATION FOR RESEARCH PARTICIPANTS

Research participants should be reasonably reimbursed for costs directly incurred during the research, such as travel costs, and compensated reasonably for their 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.

Commentary on Guideline 13

General considerations. Both in observational studies and intervention research, 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), 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 amount of compensation should be proportional to the time spent for research purposes and for travel to the research site. This amount should be calculated using the minimum hourly wage in the region or country as a reference value. The obligation to reasonably reimburse and compensate participants arises even when study enrolment offers participants potential individual benefits (for example, an investigational drug). This is because the vast majority of clinical research studies involve research procedures that have no potential individual 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 research interventions may cause more harm than good.

Appropriate compensation. Participants must also be reasonably compensated for their inconvenience and time spent participating in research according to monetary value of the country in which the research is conducted. Compensation can be monetary or non-monetary and may include, for example, health services unrelated to the research, medical insurance, educational materials, counselling or food supplies. Especially when the research poses low risks, providing compensation for participation should not raise concerns about undue inducement.

Unacceptable compensation. Compensation is not meant to compensate for risk that participants agree to undertake but rather, for inconvenience and time. Therefore, the level of compensation

should not be related to the level of risk that participants agree to undertake. But especially as the risks of research procedures having no potential individual benefit for participants increase, so does the concern that compensation may constitute an undue inducement. 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 determine whether undue inducement exists, in part because the compensation that makes some people 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 order to determine whether the average participant expected to enrol in the study is likely to participate in the research against his or her better judgment because of the compensation offered. The appropriateness of compensation is likely better judged by local research ethics committees than by international ones. Consultation with the local community may help to ascertain this even in the case of research conducted in the researcher’s own community.

Compensation for persons who are incapable of giving informed consent. Persons who are incapable of giving informed consent may be vulnerable to exploitation for financial gain by their guardians. A legally authorized representative asked to give permission on behalf of a person who is incapable of giving informed consent 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 incapable of giving informed consent, compensation must be provided in a way that participants themselves can benefit from it.

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 person is withdrawn from a study 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 – Treatment and compensation for research-related harms. When researchers must withdraw a participant from the study for wilful 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 or most of the money 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 in 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 health care and continuing treatment) or 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.

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 are 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 resulting from 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 determine whether there is an adequate arrangement for treatment and compensation for research-related 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. Dependents of participants are also entitled to material compensation for death or disability occurring as a direct result of study participation. Lack of 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 continuity of care for participants' health needs related to research harms is guaranteed without any cost to the participant for as long as such care is needed (see Guideline 6 – Caring for participants' health needs). The sponsor must provide this treatment or rehabilitation free of charge, 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. Alternatively, the sponsor may 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 to cover compensation, independent of proof of fault. Arrangements for free treatment and compensation should be described in the protocol and the informed consent.

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 is considered a consequence of the intervention when the harm would not have occurred 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 to expect in the context of clinical care. Compensation must be equitable: researchers and sponsors do not have an obligation to pay for care for every harm that befalls a participant while in a study. The research ethics committee must be satisfied that there is an adequate arrangement for free treatment and compensation for research-related harms, and provide oversight to ensure that researchers report such harms, how treatment is being paid for and compensation 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 not contain statements that would absolve a researcher from responsibility in the case of harm, or that would imply that participants waive their right to seek compensation (see Guideline 9 – Individuals capable of giving informed consent). They must also be told what medical service, organization or individual will provide the treatment and what organization will be responsible for providing compensation.

GUIDELINE 15:

RESEARCH INVOLVING VULNERABLE PERSONS AND GROUPS

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.” This implies that vulnerability involves judgments about both the probability and degree of physical, psychological, or social harm, as well as a greater susceptibility to deception or having confidentiality breached. It is important to recognize that vulnerability involves not only the ability to provide initial consent to participate in research, but also aspects of the ongoing participation in research studies. 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 potential participants collectively for a particular project, researchers and others involved in research must take into account factors that render individual 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 members of entire classes of individuals as vulnerable. However, it is useful to look at the specific characteristics that may render individuals vulnerable, as this 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. Different characteristics may also co-exist, making some individuals more vulnerable than others. This is highly dependent on the context. For example, persons who are illiterate, marginalized by virtue of their social status or behaviour, or living in an authoritarian environment, may have multiple factors that make them vulnerable.

Some characteristics can make it reasonable to assume that certain individuals 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 (see Guideline 16 – Research involving adults incapable of giving informed consent, and Guideline 17 – Research involving 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, workers in settings where research studies are conducted, 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 on Guideline 9 – Individuals capable of giving informed consent). 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 commentary on Guideline 9 – Individuals capable of giving informed consent, section on *Dependent relationship*).

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 (see commentary on Guideline 9 – Individuals capable of giving informed consent, section on *Dependent relationship*). 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 women in general must not be considered vulnerable, specific circumstances in which women could be vulnerable in research include: studies with female or transsexual sex workers; research on sexual and intimate partner violence; studies with trafficked women, refugees and asylum seekers; studies of abortion in jurisdictions where abortion is illegal; and 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 – Women as research participants).

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 – Pregnant women and breastfeeding women as research participants.

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; people with incurable or stigmatized conditions or diseases; people faced with physical frailty, for example because of age and co-morbidities, individuals who are politically powerless; and members of communities unfamiliar with modern medical concepts. Furthermore, in some contexts vulnerability might be related to gender, sexuality and age.

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 consultation with relevant stakeholders, where feasible, before, during and after the conduct of the research (see Guideline 7 – Community engagement).

Special protections. Special protections for these groups can include allowing no more than minimal risks for procedures that offer no potential individual 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. Safeguards can be designed to promote voluntary decision-making, limit the potential for confidentiality breaches, and otherwise work to protect the interests of those at increased risk of harm. Research ethics committees need to be sensitive to not overly excluding people, and allow them to participate by requiring that special protections be put in place.

Group vulnerability. Despite the importance of avoiding classification of entire groups as inherently vulnerable, circumstances exist that require research ethics committees to pay special attention to research involving certain groups. In some resource-limited countries or communities, lack of access to medical care, membership in ethnic and racial minorities, or other disadvantaged or marginalized groups can be factors that constitute vulnerability. As is true of the vulnerability of individuals, the judgment that groups are vulnerable is context dependent and requires empirical evidence to document the need for special protections.

GUIDELINE 16:

RESEARCH INVOLVING ADULTS INCAPABLE OF GIVING INFORMED CONSENT

Adults who are not capable of giving informed consent must be included in health-related research unless a good scientific reason justifies their exclusion. As adults who are not capable of giving informed consent have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. 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 persons in research are therefore necessary.

Before undertaking research with adults who are not capable 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 (if any); and
- ▶ the assent of the 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.

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 enrol in the research must be respected, unless, in exceptional circumstances, research participation is considered the best available medical option for an individual who is incapable of giving informed consent.

If participants have made advance directives for participation in research while fully capable of giving informed consent, the directives should be respected.

For research interventions or procedures that have the potential to benefit adults who are incapable of giving informed consent, the risks must be minimized and outweighed by the prospect of potential individual benefit. For research interventions or procedures that have no potential individual benefits for participants, two conditions apply:

- ▶ the interventions and procedures should be studied first in persons who can give consent when these interventions and procedures target conditions that affect persons who are not capable of giving informed consent as well as those who are capable, unless the necessary data cannot be obtained without participation of persons who are incapable of giving informed consent; and

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

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, consider the treatment options, and communicate a choice. Persons should be considered capable of giving informed consent unless it is proven otherwise. A person may be incapable to give informed consent for a variety of reasons (for example, dementia, some psychiatric conditions and accidents). Persons can become capable of giving informed consent after a certain period, or they can be incapable to decide whether they should be treated for a certain disease but capable to decide whether they want to enjoy a meal. This illustrates that a lack of decisional capacity is time-, task- and context-specific.

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 incapacity to give informed consent might reasonably be expected, participants must be routinely screened. However, it is important to note that diagnosis of a mental or behavioural disorder does not necessarily imply that individuals are incapable of giving informed consent.

Potential individual benefits and risks. The potential individual benefits and risks of research with adults incapable of giving informed consent should be evaluated based on Guideline 4 – Potential individual benefits and risks of research, and Guideline 5 – Choice of control in clinical trials.

Assent and dissent. If participants cannot consent because they are incapacitated due to mental or behavioural 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 must be considered as a process (see Guideline 9 – Individuals capable of giving informed consent) that responds to changes in the person's cognitive status and is not merely the absence of dissent.

Any explicit objection by persons who are incapable to give informed consent must be respected even if the legally authorized representative has given permission. An explicit objection may be overruled if the incapacitated person needs treatment that is not available outside the context of research, prior research has demonstrated a significant benefit (see Guideline 4 – Potential individual benefits and risks of research), and the treating physician and the legally authorized representative consider the research intervention to be the best available medical option for the person lacking capacity.

Permission of a legally authorized representative. In accordance with relevant national regulations, 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 previously formed preferences and values (if any), 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 preferences regarding the individual's willingness to enrol in research or documented preferences in an advance directive should be respected. Researchers must recognize that surrogates may have their own interests that may call their permission into question. Furthermore, in situations where a legally authorized representative is not available to allow for timely enrolment, researchers may obtain the permission of a representative who is socially accepted but not formally recognized before the law.

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, for example in an advance directive.

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. The research must not be carried out if it does not have substantial support in the community concerned. (See commentary on Guideline 4 – Potential individual benefits and risks of research, section on *Risks to groups of persons*, and Guideline 7 – 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 researcher and the research ethics committee should agree to a maximum time of involvement of an individual without obtaining either the individual's own informed consent or surrogate consent if the person continues to be unable to give consent. If, by that time, there is no individual or surrogate consent, the participant should be withdrawn from the study provided that withdrawal will not make the participant worse off. The participant or the surrogate should 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 expressed preferences and values, if any.

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 reasonably possible. In addition, they must be given the opportunity to opt out of the study.

Waivers of the permission by a legally authorized representative. Research ethics committees may waive the requirement to obtain permission from a legally authorized representative if the conditions for waiving informed consent in research with participants who are capable of giving informed consent are satisfied (Guideline 10 – Modifications and waivers of informed consent).

GUIDELINE 17:

RESEARCH INVOLVING CHILDREN AND ADOLESCENTS

Children and adolescents must be included in health-related research unless a good scientific reason justifies their exclusion. As children and adolescents have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. However, their distinctive physiologies and emotional development may also place children and adolescents at increased risk of being harmed in the conduct of research. Moreover, without appropriate support, they may not be able to protect their own interests due to their evolving 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; and
- ▶ the agreement (assent) of the child or adolescent has been obtained in keeping with the child's or adolescent's capacity, after having been provided with adequate information about the research tailored to the child's or adolescent's level of maturity.

If children reach the legal age of maturity during the research, their consent to continued participation should 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 option for a child or adolescent.

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 potential individual benefit.

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

- ▶ the interventions and procedures should be studied in adults first, when these interventions and procedures target conditions that affect adults as well as children and adolescents, unless the necessary data cannot be obtained without participation of children or adolescents; and
- ▶ the risks must be minimized and no more than minimal.

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 although they were directed at diseases also occurring in childhood. In some cases, this resulted in children or adolescents being exposed to interventions that were either not effective or 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. Research ethics committees should recognize that research involving children or adolescents spans a wide range of individuals, from infants through to those just short of legal maturity, with very different physical, cognitive and emotional capacities. A nuanced approach to evaluating research with children and adolescents is therefore required.

Order of involvement in research. There is controversy over whether research must be done first in adults or adolescents before it is done in younger children. Some believe 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 that 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 or 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 acquisition of relevant data and the development of beneficial interventions for children.

The current Guidelines do not require that research first be conducted in adults if the research includes interventions that have a prospect for potential individual benefit for children and adolescents. This prospect is sufficient to justify the risks associated with the interventions and procedures, provided that the cumulative risk of all study interventions and procedures that do not have a prospect of potential individual benefit are no more than minimal. If research meets these conditions but the cumulative risk of all study interventions and procedures that do not have a prospect of potential 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 when exploring the possible toxicity of new drugs. First exploring the possible 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.

Potential individual benefits and risks. The potential individual benefits and risks of research with children or adolescents should be evaluated based on Guideline 4 – Potential individual benefits and risks of research, and Guideline 5 – Choice of control in clinical trials.

Assent. Children and adolescents who are legally 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 meaningfully engaged in the research discussion in accordance with his or her capacities. Assent must be considered as a process (see Guideline 9 – Individuals capable of giving informed consent) and is not merely the absence of dissent. 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 for children who are literate. The process of obtaining assent must take into account not only the age of children, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation.

As adolescents near the age of majority, their agreement to participate in research may be ethically (though not legally) equivalent to consent. In this situation, parental consent is ethically best considered as “co-consent” but legally, the adolescent's agreement remains assent. If child or adolescent participants reach the legal age of majority according to applicable law and become capable of independent informed consent during the research, their written 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,” meaning 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 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 option for the given child or adolescent. In such cases, 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 a 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' decision must be overridden if the researcher believes it is not in the child's best clinical interest to enrol or continue study participation.

Permission of a parent or legally authorized representative. 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 capable 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 never sufficient to permit participation in research unless it is supplemented by the permission of a parent, legal guardian or other duly authorized representative. The decision to continue or discontinue participation by children or adolescents who become legally capable 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 not feasible or is 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 topic of the research may place the children or adolescents at risk of questioning, intimidation, or even physical harm by their parents.

In such cases, special protections to promote the best interests of these children or adolescents should 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.

A research ethics committee may also allow a waiver of parental permission if the conditions set out in Guideline 10 – Modifications and waivers of informed consent - are satisfied.

Observation of the study by a parent or guardian. A parent or legally appointed guardian who gives permission for a child or adolescent to participate in research must generally be given the opportunity, to a reasonable extent and without violating the privacy of other study participants, to observe the child’s participation as the study proceeds. This could enable the child to be withdrawn if the parent or guardian decides it is in the child’s best interests to do so.

Emergency care situations in which the researcher anticipates that children and adolescents will participate. When children and adolescents participate in emergency care research, the principles of Guideline 16 – Research involving adults incapable of giving informed consent - apply.

GUIDELINE 18:

WOMEN AS RESEARCH PARTICIPANTS

Women must be included in health-related research unless a good scientific reason justifies their exclusion. Women have been excluded from much health-related research because of their child-bearing potential. As women have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. Only the informed consent of the woman herself should be required for her research participation. Since some societies lack respect for women's autonomy, in no case must the permission of another person replace the requirement of individual informed consent by the woman.

Women of child-bearing potential must be informed in advance of the possibility of risks to the fetus should they become pregnant during their research participation. When participation in research might be hazardous to a fetus or a woman if she becomes pregnant, sponsors and researchers must guarantee access to pregnancy tests, effective contraceptive methods before and during the research and to safe, legal abortion.

Commentary on Guideline 18

General considerations. Women in many societies have been excluded from research. For example, most of the early cardiovascular disease studies have excluded women because these diseases were believed to be uncommon in women. 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 (see Guideline 15 – Research involving vulnerable persons and groups). 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. For example, heart attacks in women are different from heart attacks in men, so research is necessary to determine the best means of diagnosis and treatment in women.

Vulnerability of women. Despite the current general presumption that favours the inclusion of women in research, in many societies women remain socially vulnerable in the conduct of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions, and a cultural tendency to deny or tolerate pain and suffering. When women in these situations are potential participants in research, researchers, sponsors and ethics committees must take special care in the research design, assessment of risks and benefits, as well as the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on information provided to them.

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 behavioural research involving sex workers or women who inject drugs; and studies that solicit information about sexual behaviour. 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. 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. 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 counselling if the need arises.

Informed consent and authorization. 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 enrol.

Inclusion of women of child-bearing potential. 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 to self-determination. Although women of child-bearing 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 19 – Pregnant women and breastfeeding women as research participants). Access to a pregnancy test, to effective contraceptive methods and to safe, legal abortion must be guaranteed before exposure to a potential teratogenic or mutagenic intervention. When effective contraception and safe abortion are not available and alternative study sites are not feasible, the informed consent discussion must include information about the risk of unintended pregnancy, the legal grounds for abortion, and information about reducing harms from unsafe abortion and subsequent complications. 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 terminating 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, pregnant women must be removed from the study, and followed up and provided care through the duration of their pregnancy and delivery. Access to diagnostic tests must be provided to reveal any fetal anomalies. If anomalies are detected, women who wish may be referred for an abortion. When there is no evidence on the basis of which a potential harm to the fetus can be assumed, women who become pregnant should not automatically be removed from the study, but must be offered the option to continue or end their participation. For instance, in some cases it may be appropriate for a woman to stay in the study for safety monitoring but removed from the study drug. If the woman opts for continued participation, researchers and sponsors must offer adequate monitoring and support.

GUIDELINE 19:

PREGNANT AND BREASTFEEDING WOMEN AS RESEARCH PARTICIPANTS

Pregnant and breastfeeding women have distinctive physiologies and health needs. Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted. Research in pregnant women must be initiated only 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 breastfeeding woman.

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

For research interventions or procedures that have no potential individual benefits for pregnant and breastfeeding women:

- ▶ **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 breastfeeding women or their fetuses or infants.**

When the social value of the research for pregnant or breastfeeding women or their fetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-breastfeeding women, a research ethics committee may permit a minor increase above minimal risk.

Short-term and long-term follow-up of the fetus and the child may be required in research involving pregnant and breastfeeding women depending upon the study intervention and its potential risks.

As a general rule, health-related research involving pregnant women that has the potential for harm to the fetus should 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 breastfeeding women, but most often do so in the absence of studies involving such women and without adequate evidence of safety and efficacy. Such routine treatment includes medications that may have a prospect of serious harm to the fetus, such as radiation or chemotherapy for cancer. 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 individual benefits and harms to themselves, their fetuses and their future children. Therefore, after careful consideration of the best available relevant data, it is imperative to design research for pregnant and breastfeeding women to learn about the currently unknown risks and potential individual 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 health-related 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 breastfeeding women should be promoted in the following areas:

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

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

Researchers and research ethics committees must ensure that potential research participants are adequately informed about the risks to breastfeeding women and their infants, and about the risks to pregnant women (including future fertility), their pregnancies, their fetuses, and their future offspring. Information must also include steps taken to maximize potential individual benefits and minimize risks (see Guideline 4 – Potential individual benefits and risks of research). When evidence concerning risks is unknown or conflicting, this must be disclosed to the pregnant or breastfeeding woman as part of the informed consent process. She is the one to make the final decision about the acceptability of these risks to 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 potential 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 potential individual benefit to the fetus but 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. Adverse events associated with research in pregnancy and during lactation may not occur immediately.

Potential individual benefits and risks. The potential individual benefits and risks of research with pregnant and breastfeeding women should be evaluated based on Guideline 4 – Potential individual benefits and risks of research, and Guideline 5 – Choice of control in clinical trials.

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 an unwanted fetus to term and deliver an affected baby against their wishes. Before pregnant women are enrolled, researchers must, at a minimum, determine whether fetal impairment and mental health conditions are recognised as legal grounds for abortion in that jurisdiction. If they are not, 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 women and the women are informed about existing restrictions on abortion and possible options for obtaining an abortion in another country.

Breastfeeding women. The father may need to be consulted in research involving breastfeeding women, in accordance with Guideline 17 – Research involving children and adolescents. If a breastfed infant may be exposed to an investigational product through the ingestion of breast milk (or it is unknown whether an infant would be exposed), such research should be conducted in accordance with Guideline 17 – Research involving children and adolescents.

GUIDELINE 20:

RESEARCH IN DISASTERS AND DISEASE OUTBREAKS

Disasters arising from events such as earthquakes, tsunamis or military conflicts, and disease outbreaks, can have a sudden and devastating impact on the health of large affected populations. In order to identify effective ways of mitigating the health impact of disasters and disease outbreaks, health-related research should form an integral part of disaster response. However, the conduct of research must not unduly impact the response to the victims of a disaster.

In the conduct of research in disasters and disease outbreaks, it is essential to uphold the ethical principles embodied in these Guidelines. Conducting research in these situations raises important challenges such as the need to generate knowledge quickly, maintain public trust, and overcome practical obstacles to implementing research. These challenges need to be carefully balanced with the need to ensure the scientific validity of the research and uphold ethical principles in its conduct.

Researchers, sponsors, international organizations, research ethics committees and other relevant stakeholders should ensure that:

- ▶ studies are designed so as to yield scientifically valid results under the challenging and often rapidly evolving conditions of disasters and disease outbreaks (see Guideline 1 – Scientific and social value and respect for rights);
- ▶ the research is responsive to the health needs or priorities of the disaster victims and affected communities and cannot be conducted outside a disaster situation (see Guideline 2 – Research conducted in low-resource settings);
- ▶ participants are selected fairly and adequate justification is given when particular populations are targeted or excluded, for example health workers (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research);
- ▶ the potential burdens and benefits of research participation and the possible benefits of the research are equitably distributed (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research);
- ▶ the risks and potential individual benefits of experimental interventions are assessed realistically, especially when they are in the early phases of development (see Guideline 4 – Potential individual benefits and risks of research);
- ▶ communities are actively engaged in study planning in order to ensure cultural sensitivity, while recognizing and addressing the associated practical challenges (see Guideline 7 – Community engagement);
- ▶ the individual informed consent of participants is obtained even in a situation of duress, unless the conditions for a waiver of informed consent are met (see Guideline 9 –

Individuals capable of giving informed consent, and Guideline 10 – Modifications and waivers of informed consent); and

- ▶ **research results are disseminated, data are shared, and any effective interventions developed or knowledge generated are made available to the affected communities (see Guideline 2 – Research conducted in low-resource settings, and Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols).**

Research in disasters and disease outbreaks should ideally be planned ahead. Health officials and research ethics committees should develop procedures to ensure appropriate, expedient 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.

Sponsors and research ethics committees should evaluate and seek to minimize the risks to researchers and health professionals conducting research in a disaster context. Sponsors should include in the protocol a plan for mitigating adverse events. Furthermore, appropriate resources for mitigation measures should be included in the protocol budget.

Commentary on Guideline 20

Humanitarian response and research in the acute phase of disasters and diseases outbreaks.

Disasters are sudden events that cause great suffering or loss of life. Disease and illness can either be the cause or a result of disasters. 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 acute disaster situations is to respond to the needs of those affected. At the same time, an obligation exists 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. This is because humanitarian response and health-related research often rely on the same infrastructure and the same personnel, so priorities between the two may need to be set. If nurses and physicians become researchers, this may also create dependent relationships (see Guideline 9 – Individuals capable of giving informed consent). 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 contribute to the infrastructure for the humanitarian response and integrate their research activities with this response. Importantly, 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 considerable pressure to conduct research. This is especially the case for diseases that have a high mortality rate and where the treatment options are limited (for example during the 2014 Ebola outbreak). Conversely, in natural or man-made disasters, research can be met with great scepticism or even hostility, and researchers can be at risk of physical harm. Researchers and sponsors must be equipped to negotiate these pressures in what are typically fragile political and social situations. They must also have sufficient operational and security support in order to work effectively in such challenging environments. Acute 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 or damaged health infrastructures can challenge implementation of preferred study designs and data collection. Moreover, efforts to make available as soon as possible any interventions or products developed from the research to the affected communities are often more challenging in acute disaster situations (see Guideline 2 – Research conducted in low-resource settings). Despite these 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, an acute disaster situation can *require* modifying standard procedures so that 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 studies can begin as soon as possible without compromising ethical requirements (see below).

While all ethical principles in these Guidelines have to be upheld, some require special attention.

Potential individual benefits and risks of investigational interventions and emergency use outside clinical trials. Especially when disasters are caused by infectious diseases that are highly contagious or serious (for example influenza, Ebola), there is great pressure to develop effective treatments and vaccines. When facing a serious, life-threatening infection, 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 individual benefits and risks of experimental interventions and communicate these clearly to potential participants and individuals at risk. Even in ordinary circumstances, many promising experimental agents may not be safe and effective, and experimental interventions must be systematically evaluated in clinical trials. Moreover, emergency use can compromise recruitment of research participants and therefore undermine the conclusion of trials. Widespread emergency use with inadequate 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 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research). Especially in dire emergencies, well-off and well-connected patients must not be further privileged (for example, community leaders). Moreover, the exclusion of especially vulnerable populations must be justified (Guideline 15 – Research involving vulnerable persons and groups). It may be acceptable to prioritize certain populations in study enrolment. For example, front line workers often put themselves at risk during a disaster such as an epidemic, and if experimental interventions are effective, these workers would be able to help more patients. The principles of reciprocity and helping the largest number of people could therefore justify their prioritization. Researchers, sponsors, and research ethics committees also need to ensure that burdens and benefits of participation are equitably distributed (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research).

Scientific validity and alternative trial designs. Disasters unfold quickly and study designs need to be chosen so that studies will yield meaningful data in a rapidly evolving situation. 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 not be conducted (see Guideline 1 – Scientific and social value and respect for rights). Research may even divert personnel or resources from the disaster response. In clinical trials, the randomised-controlled trial design is often considered 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 still 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,

a variation in critical background factors (for example mortality and infection rates), and measurement of outcomes, among others. 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 at an early stage is essential for maintaining public trust and ensuring that studies are conducted in a culturally sensitive manner (see Guideline 7 – Community engagement). Researchers and sponsors can use creative mechanisms to expedite and facilitate community engagement in a disaster situation (for example, by using social media). Fostering community leadership will often be important to address distrust and communicate effectively in order to gain support for the study design. In engaging with communities, researchers, sponsors and research ethics committees should be aware of potential conflicts of interest vis-à-vis the proposed research. For example, community leaders might seek to reassert their own authority by providing services to their communities through research.

Ethical review and oversight. The standard mechanism for ethical review will often be too time-consuming to enable full research protocols to be prepared and reviewed at the outset of a disaster. Procedures should be developed to facilitate and accelerate ethical review in a situation of crisis. 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 should ideally be planned in advance. This can involve, among other things, submitting partial study protocols for ethical “pre-screening” and drafting arrangements for data and sample sharing among collaborators. Health officials might also create an international network of specialists that could assist local review during a disaster. However, reviewing generic research protocols in advance cannot substitute for the ethical review of specific research protocols in a disaster. Local ethics review should be carried out whenever possible.

Informed consent. Even though most disaster victims are under duress, it is important to obtain their informed consent for study participation and especially to emphasize the difference between research and humanitarian aid. To explain the difference 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 prevent them from making a voluntary decision (Guideline 9 – Individuals capable of giving informed consent). The informed consent process must be designed in a way that is comprehensible and sensitive to persons who are under duress.

Special protections for individuals incapable of giving informed consent may apply, as described in Guideline 16 – Research involving adults incapable of giving informed consent, in the section on *Emergency care situations in which the researcher anticipates that many participants will be unable to consent*.

Individual informed consent may be waived for the sharing and analysis of surveillance data provided that the conditions of Guideline 10 – Modifications and waivers of informed consent - are met and appropriate governance systems for these data are put in place.

GUIDELINE 21:

CLUSTER RANDOMIZED TRIALS

In advance of initiating a cluster randomized trial, researchers, sponsors, relevant authorities, and research ethics committees should:

- ▶ **determine who are the research participants and what other individuals or groups are affected, even though they are not directly targeted;**
- ▶ **determine whether it is required or feasible to obtain informed consent from patients, health care workers, or community members 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 a particular cluster randomized trial; and**
- ▶ **decide whether permission must be obtained from a gatekeeper.**

Commentary on Guideline 21

General considerations. In this research design, groups of individuals (clusters), communities, hospitals, or units of a health facility are randomized to different interventions. The same ethical principles that govern all health-related research with humans are applicable to cluster randomized trials (CRTs). However, in the context of CRTs, these principles may require further specification as set out in this Guideline.

Determining 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 CRTs, the subjects can be patients, health care workers, or both. In CRTs in which health-care workers are the subjects, the intervention may not be targeted at patients, 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 regarding the number of infections are recorded, patients are not subjects in this type of study.

Informed consent. As a general rule, researchers must obtain informed consent from participants in a cluster randomized study unless a waiver or modification of consent is granted by a research ethics committee (see Guideline 10 – Modifications and waivers of informed consent). Waivers or modifications of informed consent may be necessary in some CRTs in which it is 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 centres, it could be difficult for patients to find another hospital or general practice to avoid a new method of delivery of preventive services. Another reason for the use of waivers or modifications

of consent in CRTs is that researchers may want to avoid participants in the control group learning about the intervention in the intervention group and accordingly, change their behaviour or try to get the intervention at another location, thereby compromising the results of the study.

When a study is conducted at a cluster level (different hospitals, clinics, or communities), the requirement to obtain consent from health care workers can compromise the results or make it difficult to analyse the results. When health care workers are the subjects, the refusal of some workers to be observed or to apply a new diagnostic or therapeutic tool could confound the results of the research. Researchers would not be able to tell whether a new intervention is sufficiently effective if some health care workers refuse to participate and employ their usual procedures. A waiver of consent would then be an option (see Guideline 4 – Potential individual benefits and risks of research), 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 and their consent to receive the intervention would be required.

Although in many CRTs participants cannot consent to being randomized, 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 randomized at the cluster level (for example, a vaccination campaign applied at the school level). These trials are called *individual-cluster randomized trials*. In some *individual-cluster randomized 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 randomized to a vaccination programme or to being allocated to that cluster, but they could consent or refuse to consent to their child's vaccination at school. In other CRTs, both the intervention and the community are randomized at the cluster level. These trials are called *cluster-cluster randomized trials* (for example, all the students in a school or all residents of a community). In *cluster-cluster randomized 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, individual consent for data collection procedures is usually possible in both types of cluster randomized trials.

Ethical acceptability of a no-intervention group. Some CRTs investigate interventions that have been proven to be effective elsewhere; this is termed *implementation research*. This type of research is often conducted in low-resource settings. An ethical question pertaining to this type of study is whether it is acceptable to withhold the proven intervention from a control group in a CRT. This situation is analogous to that of placebo controls in a randomized, 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 centre with a high infection rate among the patients. In the implementation CRT, 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 an established effective treatment from the control cluster.

Gatekeeping in cluster randomized trials. When a CRT 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 enrol the cluster or organization in the trial. Such permission does not replace the need to obtain individual informed consent where

this is required. Although a 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 when provided outside a research project. Moreover, the decision-maker must ensure that the risks of participation in the study and the randomisation 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 DATA OBTAINED FROM THE ONLINE ENVIRONMENT AND DIGITAL TOOLS IN HEALTH-RELATED RESEARCH

When researchers use the online environment and digital tools to obtain data for health-related research they should use privacy-protective measures to protect individuals from the possibility that their personal information is directly revealed or otherwise inferred when datasets are published, shared, combined or linked. Researchers should assess the privacy risks of their research, mitigate these risks as much as possible and describe the remaining risks in the research protocol. They should anticipate, control, monitor and review interactions with their data across all stages of the research.

Researchers should inform persons whose data may be used in the context of research in the online environment of:

- ▶ the purpose and context of intended uses of data and information;
- ▶ the privacy and security measures used to protect their data, and any related privacy risks; and
- ▶ the limitations of the measures used and the privacy risks that may remain despite the safeguards put in place.

In case of a refusal by the person approached, researchers should refrain from using the data of this individual. This informed opt-out procedure must fulfil the following conditions: 1) persons need to be aware of its existence; 2) sufficient information needs to be provided; 3) persons need to be told that they can withdraw their data; and 4) a genuine possibility to object has to be offered.

Researchers collecting data on individuals and groups through publicly accessible websites without direct interaction with persons should, at a minimum, obtain permission from website owners, post a notice of research intent, and ensure compliance with published terms of website use.

Researchers must describe in the protocol how data obtained from online environments and digital tools will be treated, along with the potential risks of the research and how the potential risks are mitigated.

Commentary on Guideline 22

General considerations. The vast range of data sources and technologies for collecting, analysing and sharing large quantities of data about individuals in the online environment has significantly expanded research opportunities, particularly with respect to studying personal and group characteristics, behaviours and interactions. The online environment includes the Internet, website platforms, social media, services such as purchasing, as well as email, chat and other applications, which are accessed by an array of computing and mobile devices. The characteristics of this environment make protecting the privacy of persons a major challenge.

People currently share information about themselves and others in their immediate circle with large numbers of other people online. This type of sharing has generated huge amounts of data for analysis by both public and private entities. Researchers can extract this information using automated tools. Such data are considered an important asset by the commercial sector for consumer profiling and marketing purposes.

The need for privacy protection. It has been argued that information posted online voluntarily by individuals is public, is used and sold by the commercial sector, and that therefore the normal protections and consent for research should not be required. However, users rarely adequately understand how their data are stored and used. And despite the insights that may result from this high volume of data, legal and ethical standards are unclear due to changing social norms and the blurring of boundaries of public and private information. Although the information may be collected from a public source, researchers should acknowledge that persons may be unwilling to have their data obtained for studies, and should account for the privacy norms in communities sharing information online. Users may not fully understand or appreciate the consequences of their actions, and may feel violated when their information is used in a context they did not anticipate.

The existence of data and information already online does not relieve the researcher from the obligation to respect privacy and mitigate risks that could result from combining data from multiple sources and their subsequent use and publication. Instead, the risk of unauthorized or inadvertent disclosure, in combination with technological capabilities that increase the volume and nature of identifiable data, point to the need to heighten data security and privacy protection in this context. It is especially important to address potential risks to vulnerable groups and others who may face adverse consequences as a result of exposure through this type of research.

Assessment of privacy risk. Assessment of privacy risk should encompass the range of threats to privacy, the aspects that exacerbate those threats, the likelihood of disclosure of information given those threats, and the extent, severity and likelihood of risks arising from those disclosures. Some privacy risks may be difficult to predict as data are accumulated, combined and used in a wide variety of contexts. For example, research on clinical or public health interventions using mobile devices is increasingly common. The convenience and reach of mobile devices, whether in the hands of persons or researchers, enables the convenient collection and rapid transmission of data in a variety of settings. Researchers using mobile phones and apps to collect data must be aware that these devices and applications each may have vastly different privacy-related characteristics and limitations.

Privacy risks are not a simple function of the presence or absence of specific fields, attributes or keywords in a set of data. Much of the potential for privacy risks stems from what can be inferred about individuals from the data as a whole or when the data are linked with other available information. Approaches to privacy protection in common use often provide limited protection. Traditional de-identification techniques have notable limitations, and definitions based on a simple concept of “identifiability” lack sufficient precision to be used as a standard. Very few data points can be used

to uniquely identify an individual in a set of data. Researchers who use only redaction of names or other clearly identifying information may reveal information that exposes individuals to privacy risks.

Mitigation of privacy risk. Selection and implementation of appropriate measures to mitigate privacy risks by investigators is essential and entails adopting privacy and security controls suited to the intended uses and privacy risks associated with the data. These measures in turn require a systematic analysis of the primary and secondary uses of the data, considering not just re-identification risks but also inference risks. This analysis should take into account not only whether a person can be directly associated with a particular attribute, but also the extent to which attributes that may be revealed or inferred depend on an individual's data and the potential harm that may result. It also takes into account the potential uses of the data, which in turn affects data management, output, and the privacy controls that may ultimately be suitable. The types of uses or analytic purposes intended impact the choice of privacy controls at each stage, as some techniques may enable or restrict certain types of uses.

Researchers should identify and manage risks during data collection, processing and dissemination. Privacy considerations require a conservative approach to data dissemination on the Internet. Academic publications and some institutions often require researchers to make their datasets publicly available, sometimes in an open data format. Public disclosure in such formats is problematic for datasets that contain identifiers, key-attributes and secondary attributes, as these enable re-identification of subjects by linking the records with auxiliary datasets. Once a dataset is released online, the researcher has lost control over how the data will be used, and the context of uses may change.

Guidance to research ethics committees. Research ethics committees may wish to consult a regularly updated list of specific privacy and security measures such as the one envisaged by WHO, that would be deemed to satisfy the requirement for reasonable and appropriate safeguards. There should be a requirement for implementing these safeguards broadly, covering some categories of research activities that may fall within an exemption to research ethics committee review. Research ethics committees should understand the application of controls that are calibrated to different categories of data sharing (meaning in some cases, data shared publicly would be subject to more stringent requirements than data shared among researchers). In efforts to harmonize approaches across regulations and institutional policies, research ethics committees should emphasize the need to provide similar levels of protection to research activities that pose similar privacy risks.

GUIDELINE 23:

REQUIREMENTS FOR ESTABLISHING RESEARCH ETHICS COMMITTEES AND FOR THEIR REVIEW OF PROTOCOLS

All proposals to conduct health-related research involving humans must be submitted to a research ethics committee to determine whether they qualify for ethical review and to assess their ethical acceptability, unless they qualify for an exemption from ethical review (which may depend upon the nature of the research and upon applicable law or regulations). The researcher must obtain approval or clearance by such a committee before beginning the research. The research ethics committee should conduct further reviews as necessary, for example, when 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 should establish efficient communication in cases of externally sponsored and multi-centre research. In externally sponsored research, ethical review must take place in both the host and the sponsoring institution.

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

Commentary on Guideline 23

General considerations. Research ethics committees may function at the institutional, local, regional, or national levels, 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 governments must allocate sufficient resources for the ethical review process. Contributions of study sponsors to institutions or governments to support ethics review must be transparent.

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 (see Guideline 1 – Scientific and social value and respect for rights). The ethical review must consider, among other aspects: the study design; provisions for minimizing risk; an appropriate balance of risks in relation to potential individual benefits for participants and the social value of the research; safety of the study site, medical interventions, and monitoring safety during the study; and the feasibility of the research. Scientifically unsound research involving humans is unethical in that it may expose them to risk or inconvenience for no purpose. Even if there is no risk of injury, involving persons' 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 design and 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 (sometimes called expedited 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 committee members required for accelerated review; and
- ▶ 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 require re-consent by participants, affect the safety of participants, or other ethical matters that emerge during the course of the study. These further reviews include progress reports submitted by researchers 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. Membership normally must include physicians, scientists and other professionals such as research coordinators, nurses, lawyers, and ethicists, as well as community members or representatives of patients' groups who can represent the cultural and moral values of study participants. Ideally, one or more members should have experience as study participants since there is growing recognition that knowledge gained through personal experience as a participant can supplement the professional understanding of illness and medical care. 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 of relevant advocacy groups should be invited to meetings where such protocols will be reviewed (see

Guideline 15 – Research involving vulnerable persons and groups). 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. Committees must keep records of their deliberations and decisions.

Conflicts of interests on the part of committee members. Research ethics committees must provide independent ethical opinions. Pressure can be brought to bear from many different directions, not just financial. Research ethics committees must therefore 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 – Conflicts of interest). Research ethics committees may receive a fee for reviewing studies. However, this need not constitute a conflict of interest (see Guideline 25 – Conflicts of interest).

National (centralized) or local review. Research ethics committees may be created under the aegis of national or local 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 scientific and 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 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 health-related research is carried out within a defined geographical area or network.

Externally sponsored research. Research may be externally sponsored, meaning 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 – Collaborative partnership and capacity building for research and review). Researchers and sponsors who plan to perform research in settings where research ethics committees are absent or lack adequate training should help to establish such committees according to their ability before the research is initiated, and make provisions for their education in research ethics (see Guideline 8 – Collaborative partnership and capacity building for research and review).

Externally sponsored research must be reviewed at the site of the sponsor as well as locally. The ethical standards should be no less stringent than they would be for research carried out in the country of the sponsoring organization (see also Guideline 2 – Research conducted in low-resource settings). 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 are valid, the study must be conducted in a methodologically identical way at each centre. However, committees at individual centres must be authorized to adapt the informed consent document provided by the sponsor or the lead institution in the multi-centre trial in order to make it culturally appropriate.

To avoid lengthy procedures, multi-centre research in a single jurisdiction (state or country) should be reviewed by only one research ethics committee. In cases of multi-centre research, if a local

review committee proposes changes to the original protocol that it believes are necessary to protect the research participants, these changes must be reported to the research institution or sponsor responsible for the whole research programme for consideration and possible action. This should ensure that all persons are protected and that the research will be valid across sites.

Ideally, review procedures should be 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 must be sensitive to increases in risk of harm or wrongs to local participants and populations.

Exemptions from review. Some studies may be exempt from review. For example, when publicly available data are analysed or the data for the study are generated by observation of public behaviour, and data that could identify individual persons or groups are anonymized or coded, the study may be exempt. Health systems research may be exempted from review if public officials are interviewed in their official capacity on issues that are in the public domain.

Monitoring. Research ethics committees must be authorized to monitor ongoing studies. The researcher must provide relevant information to the committee to permit monitoring of research records, especially information about any serious adverse events. Following the analysis of the study data, researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

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 decide whether a deviation is legitimate or illegitimate. Protocol violations are deviations from the original protocol that significantly affect the rights or interests of research participants and significantly impact the scientific validity of the data. In the case of protocol violations, research ethics committees should ensure that study participants will be informed and provision will be made for the protection of their safety and welfare.

A researcher may fail to submit a protocol to a research ethics committee for prospective review. This omission is a clear and serious violation of ethical standards, unless applicable regulations specify conditions for exemptions from review.

Research ethics committees generally do not have the 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 the sponsor and 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

Public accountability is necessary for realizing the social and scientific value of health-related research. Therefore, researchers, sponsors, research ethics committees, funders, editors and publishers have an obligation to comply with recognized publication ethics for research and its results.

Researchers should 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 should be published or otherwise be made publicly available. Any publication or report resulting from a research study should indicate which research ethics committee has authorized the study.

Researchers and sponsors should also share information about and data from past research.

Commentary on Guideline 24

General considerations. In order to maximize benefits accruing from health research, reduce risks to future volunteers from undisclosed harms identified in previous clinical studies, reduce biases in evidence-based decision-making, improve efficiency of resource allocation for both research and development and financing of health interventions and promote societal trust in health-related research, researchers, sponsors, research ethics committees, funders, editors and publishers have an obligation to ensure public accountability. 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 alleviate pain and suffering (see Guideline 1 – Scientific and social value and respect for rights). Health-related research plays a vital role in this effort 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 functions well only 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 to ensure the public accountability of research. This includes obligations to prospectively register studies (for example, in clinical trials registries), publish their results, and share the data on which these results are based. Moreover, given that many results from past research remain unpublished, retrospective registration in registries should be a priority so that clinicians, patients, sponsors and researchers can request disclosure of methods and results.

Trial registries. 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 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 health-related research enables comparison of data reported with hypotheses the protocol was initially designed to test and helps to determine 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 involving human beings 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 accepted guidelines, such as those of the International Committee of Medical Journal Editors (ICMJE) for ethical reporting. Sources of funding, institutional affiliations and conflicts of interest must be disclosed in the publication. Reports of research that fail to comply with 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 analyse the data independently, prepare manuscripts, or publish them. Researchers must also communicate the results of their work to the lay public. Ideally, researchers should take steps to promote and enhance public discussion. Knowledge resulting from the research should be made accessible to the communities in which the research was conducted, either through publication in scientific journals or through other channels (see Guideline 2 – Research conducted in low-resource settings).

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 requires careful balancing of competing considerations. Sharing of study data presents risks, burdens, and challenges as well potential individual 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 analyse 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.

It is crucial 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 must 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 to share data. In their review of protocols, research ethics committees should consider a researcher's and sponsor's record in reporting results. Medical journals should request that authors share the analytical data set supporting the publication 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 by controlling with whom the data are shared and under what conditions, without compromising the scientific usefulness of the shared data. Organizations that share data should employ 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 have other interests (for example, 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 should take the following steps:

- ▶ Research institutions should develop and implement policies and procedures to mitigate conflicts of interest and educate their staff about such conflicts;
- ▶ Researchers should ensure that the materials submitted to a research ethics committee include a disclosure of interests that may affect the research;
- ▶ Research ethics committees should 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; and
- ▶ Research ethics committees should require their members to disclose their own interests to the committee and take appropriate means of mitigation in case of a conflict of interest (see Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols).

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 the 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. This 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 overly 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 example, 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 "finder's fee" may lead researchers – intentionally or unintentionally – to interpret the inclusion or exclusion criteria of a study too flexibly, thereby potentially exposing participants to excessive risks or compromising the scientific validity of the research. This situation is of particular concern when participants are dependent on a researcher who is also their clinician (see Guideline 9 – Individuals capable of giving informed consent, section on *Dependent relationship*), and when the salary of the clinician is considerably lower than what the researcher is paid. It may also lead researchers to pressure eligible participants to enrol, 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 company sponsoring the research, such as stock ownership.

- 2. Research institutions (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 employees. 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. Pharmaceutical companies may feel pushed to accelerate a marketing authorization for getting a longer period of patent protection, or they may be tempted to downplay the side effects of new medicines to get broader prescription patterns.

- 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 their members receive salaries or when they are directly funded by sponsors or serve an institution that depends significantly on support from a single sponsor or several sponsors.

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

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 the sponsor's or investigator's conflicts of interest unduly compromise or undermine the ethical or scientific conduct of a study. 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 have to exercise their judgment when evaluating the seriousness of conflicts of interest.

As a general rule, a potential serious conflict of interest exists when there is a significant possibility that the actions of an investigator resulting from professional, academic, or financial interests will result in biased study results or cause harm or wrong to participants.

Conflicts of interests can influence researchers subconsciously. For example, researchers with a financial stake in a study may not intentionally manipulate the research findings. However, their financial interests may subconsciously influence their 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 this is 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 proportional to their seriousness. For example, a minor conflict of interest may be appropriately managed by disclosure, while a potential serious conflict can, in some 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 making procedures and policies effective.
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. The development of a standardized disclosure form and related educational and explanatory materials may help to ensure that researchers understand conflicts of interest and routinely report relevant facts about their own situation to research ethics committees reviewing their protocols. Disclosure forms should provide a definition of conflicts of interest, along with some examples, and help researchers 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 materials submitted to the committee, the member of the research team with the apparent conflict should be contacted for further information. Research ethics committees may also consult with the Conflict of Interest Coordinator in their institution.
3. **Disclosure of interests to participants.** Research ethics committees may require that conflicts of interest be disclosed 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 2). In the case of serious conflicts of interest, studies suggest that disclosure works best when it is provided by a health professional 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 be involved only as a collaborator or consultant for specific tasks that require such

expertise, but not as a principal investigator 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 – Requirements for establishing research ethics committees and for their review of protocols).

APPENDIX 1

ITEMS TO BE INCLUDED IN A PROTOCOL (OR ASSOCIATED DOCUMENTS) FOR HEALTH-RELATED RESEARCH INVOLVING HUMANS

(Include the items relevant to the study/project in question)

1. Title of the study;
2. A summary of the proposed research in lay/non-technical language;
3. A clear statement of the justification for the study, its significance in development and in meeting the needs of the country /population in which the research is carried out;
4. The investigators` views of the ethical issues and considerations raised by the study and, if appropriate, how it is proposed to deal with them;
5. Summary of all previous studies on the topic, including unpublished studies known to the investigators and sponsors, and information on previously published research on the topic, including the nature, extent and relevance of animal studies and other preclinical and clinical studies (Guideline 4);
6. A statement that the principles set out in these Guidelines will be implemented;
7. An account of previous submissions of the protocol for ethical review and their outcome;
8. A brief description of the site(s) where the research is to be conducted, including information about the adequacy of facilities for the safe and appropriate conduct of the research, and *relevant* demographic and epidemiological information about the country or region concerned;
9. Name and address of the sponsor;
10. Names, addresses, institutional affiliations, qualifications and experience of the principal investigator and other investigators (Guideline 1);
11. The objectives of the trial or study, its hypotheses or research questions, its assumptions, and its variables (Guideline 1);
12. A detailed description of the design of the trial or study. In the case of controlled clinical trials the description should include, but not be limited to, whether assignment to treatment groups

- will be randomized (including the method of randomization), and whether the study will be blinded (single blind, double blind), or open (Guideline 5);
13. The number of research participants needed to achieve the study objective, and how this was statistically determined;
 14. The criteria for inclusion or exclusion of potential participants, and justification for the exclusion of any groups on the basis of age, sex, social or economic factors, or for other reasons (Guideline 3);
 15. The justification for involving as research participants children or adolescents, persons who are unable to give informed consent or vulnerable persons or groups, and a description of special measures to minimize risks to such persons (Guidelines 15, 16 and 17);
 16. The process of recruitment, e.g. advertisements, and the steps to be taken to protect privacy and confidentiality during recruitment (Guideline 3);
 17. Description and explanation of all interventions (the method of treatment administration, including route of administration, dose, dose interval and treatment period for investigational and comparator products used);
 18. Plans and justification for withdrawing or withholding standard therapies in the course of the research, including any resulting risks to persons (Guidelines 4 and 5);
 19. Any other treatment that may be given or permitted, or contraindicated, during the study (Guideline 6);
 20. Clinical and laboratory tests and other tests that are to be carried out;
 21. Samples of the standardized case-report forms to be used, the methods of recording therapeutic response (description and evaluation of methods and frequency of measurement), the follow-up procedures, and, if applicable, the measures proposed to determine the extent of compliance of persons with the treatment;
 22. Rules or criteria according to which participants may be removed from the study or clinical trial, or (in a multi-centre study) a centre may be discontinued, or the study may be terminated;
 23. Methods of recording and reporting adverse events or reactions, and provisions for dealing with complications (Guidelines 4 and 23);
 24. The known or foreseen risks of adverse reactions, including the risks attached to each proposed intervention and to any drug, vaccine or procedure to be tested (Guideline 4);
 25. The potential individual benefits of the research to participants and to others (Guideline 4);
 26. The expected benefits of the research to the population, including new knowledge that the study might generate (Guidelines 1 and 4);
 27. For research carrying more than minimal risk of physical injury, details of plans, including insurance coverage, to provide treatment for such injury, including the funding of treatment, and to provide compensation for research-related disability or death (Guideline 14);

28. Provision for continued access to study interventions that have demonstrated significant benefit, indicating its modalities, the parties involved in continued care and the organization responsible for paying for it, and for how long it will continue (Guideline 6);
29. For research on pregnant women, a plan, if appropriate, 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 child (Guideline 19);
30. The means proposed to obtain individual informed consent and the procedure planned to communicate information to prospective participants, including the name and position of the person responsible for obtaining consent (Guideline 9);
31. When a prospective subject is not capable of informed consent, satisfactory assurance that permission will be obtained from a duly authorized person, or, in the case of a child who is sufficiently mature to understand the implications of informed consent but has not reached the legal age of consent, that knowing agreement, or assent, will be obtained, as well as the permission of a parent, or a legal guardian or other duly authorized representative (Guidelines 16 and 17);
32. An account of any economic or other inducements or incentives to prospective participants to participate, such as offers of cash payments, gifts, or free services or facilities, and of any financial obligations assumed by the participants, such as payment for medical services;
33. Plans and procedures, and the persons responsible, for communicating to participants information arising from the study (on harm or benefit, for example), or from other research on the same topic, that could affect participants' willingness to continue in the study (Guideline 9);
34. Plans to inform participants about the results of the study;
35. The provisions for protecting the confidentiality of personal data, and respecting the privacy of persons, including the precautions that are in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives without the consent of the subject (Guidelines 4, 11, 12 and 24);
36. Information about how the code, if any, for the persons' identity is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency (Guidelines 11 and 12);
37. Any foreseen further uses of personal data or biological materials (Guidelines 11 and 12);
38. A description of the plans for statistical analysis of the study, including plans for interim analyses, if any, and criteria for prematurely terminating the study as a whole if necessary (Guideline 4);
39. Plans for monitoring the continuing safety of drugs or other interventions administered for purposes of the study or trial and, if appropriate, the appointment for this purpose of an independent data-monitoring (data and safety monitoring) committee (Guideline 4);
40. A list of the references cited in the protocol;
41. The source and amount of funding of the research: the organization that is sponsoring the research and a detailed account of the sponsor's financial commitments to the research institution, the investigators, the research participants, and, when relevant, the community (Guideline 25);

42. The arrangements for dealing with financial or other conflicts of interest that might affect the judgement of investigators or other research personnel: informing the institutional conflict-of-interest committee of such conflicts of interest; the communication by that committee of the pertinent details of the information to the ethical review committee; and the transmission by that committee to the research participants of the parts of the information that it decides should be passed on to them (Guideline 25);
43. For research that is to be carried out in a low-resource setting, the contribution that the sponsor will make to capacity-building for scientific and ethical review and for health-related research in the host country, and an assurance that the capacity-building objectives are in keeping with the values and expectations of the participants and their communities (Guideline 8);
44. The research protocol or documents sent to the research ethics committee should include a description of the plan for (continued) community engagement, and present resources allocated for the community engagement activities. This documentation must clarify what has been and will be done, when and by whom to ensure that the community is clearly mapped and defined and can be proactively engaged throughout the research to ensure that the research is relevant to the community and is accepted. The community should participate, when feasible, in the actual discussion and preparation of the research protocol and documents (Guideline 7);
45. Particularly in the case of an industrial sponsor, a contract stipulating who possesses the right to publish the results of the study, and a mandatory obligation to prepare with, and submit to, the principal investigators the draft of the text reporting the results (Guideline 24);
46. In the case of a negative outcome, an assurance that the results will be made available, as appropriate, through publication or by reporting to the drug registration authority (Guideline 24);
47. Plans for publication of research results in certain fields (for example, epidemiology, genetics, sociology) that may present risks to the interests of communities, societies, families, or racially or ethnically defined groups and for minimizing risks to these groups, notably by maintaining confidentiality during and after the study and publishing the resulting data in a manner that is respectful of the interests of all concerned (Guideline 4); and
48. A statement that any proven evidence of falsification of data will be dealt with in accordance with the policy of the sponsor to take appropriate action against such unacceptable procedures.

APPENDIX 2

OBTAINING INFORMED CONSENT: ESSENTIAL INFORMATION FOR PROSPECTIVE RESEARCH PARTICIPANTS

Before requesting an individual's consent to participate in research, the researcher must provide the following information, in language or another form of communication that the individual can understand (see also Guideline 9):

1. the purpose of the research, its methods, the procedures to be carried out by the researcher and the participant, and an explanation of how the research differs from routine medical care (Guideline 9);
2. that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary (Guideline 9);
3. that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled (Guideline 9);
4. the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;
5. whether money or other forms of material goods will be provided in return for the individual's participation, and, if so, the kind and amount, and that the time spent on the research and other inconveniences resulting from study participation will be appropriately compensated, monetary or non-monetary (Guideline 13);
6. that, after the completion of the study, participants will be informed of the outcomes of the research in general, if they so wish;
7. that individual participants during or after a study or collection of their biological material and health-related data will be informed of life-saving information and data of immediate clinical utility involving a significant health problem (see also Guideline 11);
8. that unsolicited findings will be disclosed if they occur (Guideline 11);
9. that participants have the right of access to their clinically relevant data obtained during a study on demand (unless the research ethics committee has approved temporary or permanent non-disclosure

- of data, in which case the participant should be informed of, and given, the reasons for such non-disclosure);
10. pain and discomfort of experimental interventions, known risks and possible hazards, to the individual (or others) associated with participation in the research, including risks to the health or well-being of a participant's direct relatives (Guideline 4);
 11. the potential clinical benefits, if any, expected to result to participants from participating in the research (Guidelines 4 and 9);
 12. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge (Guideline 1);
 13. how the transition to care after research is arranged and to what extent they will be able to receive beneficial study interventions post-trial and whether they will be expected to pay for them (Guidelines 6 and 9);
 14. the risks of receiving unregistered interventions if they receive continued access to a study intervention before regulatory approval (Guideline 6);
 15. any currently available alternative interventions or courses of treatment;
 16. new information that may have come to light, either from the study itself or other sources (Guideline 9);
 17. the provisions that will be made to ensure respect for the privacy of participants, and for the confidentiality of records in which participants are identified (Guidelines 11 and 22);
 18. the limits, legal or other, to the researchers' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality (Guidelines 12 and 22);
 19. the sponsors of the research, the institutional affiliation of the researchers, and the nature and sources of funding for the research, and, when they exist, any conflicts of interest of researchers, research institutions and research ethics committees and how these conflicts will be managed (Guidelines 9 and 25);
 20. whether the researcher is serving only as a researcher or as both researcher and the participant's physician (Guideline 9);
 21. the extent of the researcher's responsibility to provide care for participants' health needs during and after the research (Guideline 6);
 22. that treatment and rehabilitation will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the medical service or organization that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment (Guideline 14);
 23. in what way, and by what organization, the participant or the participant's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation) (Guideline 14);
 24. whether or not, in the country in which the prospective participant is invited to participate in research, the right to compensation is legally guaranteed;

25. that a research ethics committee has approved or cleared the research protocol (Guideline 23);
26. that they will be informed in case of protocol violations and how safety and welfare will be protected in such a case (Guideline 23).

In specific cases, before requesting an individual's consent to participate in research, the researcher must provide the following information, in language or another form of communication that the individual can understand:

1. for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), that the participant will not be told of the assigned treatment until the study has been completed and the blind has been broken;
2. whether all essential information is disclosed and, if not, that they are asked to agree to receiving incomplete information and that full information will be provided before study results are analysed and participants are given the possibility to withdraw their data collected under the study (Guideline 10);
3. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a participant's genetic tests to immediate family relatives or to others (e.g. insurance companies or employers) without the consent of the participant (Guideline 11);
4. the possible research uses, direct or secondary, of the participant's medical records and of biological specimens taken in the course of clinical care;
5. for collection, storage and use of biological material and health-related data, that broad informed consent will be obtained, which should specify: the purpose of the biobank, the conditions and duration of storage; the rules of access to the biobank; the ways in which the donor can contact the biobank custodian and can remain informed about future use; 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; the intended goal of such use, whether only for research, basic or applied, or also for commercial purposes, and whether the participant will receive monetary or other benefits from the development of commercial products developed from their biological specimens; the possibility of unsolicited findings and how they will be dealt with; the safeguards that will be taken to protect confidentiality as well as their limitations, whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, that participants have the right to decide about such future use, to refuse storage, and to have the material destroyed (Guidelines 11 and 12);
6. when women of childbearing potential are participating in health-related research, information about the possible risks, if they become pregnant during the research, to themselves (including future fertility), their pregnancies, their fetuses, and their future offspring; and the guaranteed access to a pregnancy test, to effective contraceptive methods and to safe, legal abortion before exposure to a potential teratogenic or mutagenic intervention. When effective contraception and/or safe abortion are not available and alternative study sites are not feasible, the women must be given information about: the risk of unintended pregnancy; the legal grounds for abortion; reducing harms from unsafe abortion and subsequent complications; and, when pregnancy is not terminated, the guarantee for a medical follow-up for their own health and that of the infant and child and the information that it is often difficult to determine causality in cases of fetal or infant abnormalities (Guidelines 18 and 19);

7. when concerning pregnant and breastfeeding women, the risks of participation in health-related research to themselves, their pregnancies, their fetuses, and their future offspring, what has been done to maximize potential individual benefits and minimize risks, that evidence concerning risks may be unknown or controversial, and that it is often difficult to determine causality in cases of fetal or infant abnormalities (Guidelines 4 and 19);
8. when concerning disaster victims who mostly are under duress, the difference between research and humanitarian aid (Guideline 20); and
9. when research is done in the online environment and using online or digital tools that may involve potentially vulnerable persons, information about the privacy and security controls that will be used to protect their data; and the limitations of the measures used and the risks that may remain despite the safeguards put in place (Guideline 22).