

55 **Guideline 1: Social value**

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

66 *Commentary on Guideline 1*

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

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

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

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

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

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

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## 112 **Guideline 2: Research conducted in low-resource settings**

113

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

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

- 119 • **Make every effort in cooperation with government and civil society to make available as**  
120 **soon as possible any intervention or product developed, and/or knowledge generated, for**  
121 **the population or community in which the research is carried out. This requirement does**  
122 **not preclude capacity building or the provision of additional benefits to the population or**  
123 **community;**
- 124
- 125 • **Consult with and inform communities about the plans for making any intervention or**  
126 **product developed intervention available, including the responsibilities of all relevant**  
127 **stakeholders.**
- 128

### 129 *Commentary on Guideline 2*

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

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

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

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

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

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

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

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

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### 210 **Guideline 3: Equitable distribution of benefits and burdens in the selection of groups of** 211 **participants in research**

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

#### 220 *Commentary on Guideline 3*

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

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

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

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

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

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

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

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#### 275 **Guideline 4: Potential benefits and risks of research**

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

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

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

- 286 • **For research interventions or procedures that have the potential to benefit participants,**  
287 **risks are acceptable if they are outweighed by the prospect of individual benefit and**  
288 **the available evidence suggests that the intervention will be at least as advantageous,**  
289 **in the light of foreseeable risks and benefits, as any established effective alternative.**  
290 **Therefore, as a general rule, participants in the control group of a trial must receive an**  
291 **established effective intervention. The conditions under which placebo may be used**  
292 **are spelled out in guideline 5.**
- 293
- 294 • **For research interventions or procedures that offer no potential benefits to**  
295 **participants, the risks must be appropriate in relation to the social value of the**  
296 **knowledge to be gained (expected benefits to society from the generalizable**  
297 **knowledge).**
- 298 • **In general, when it is not possible or feasible to obtain the informed consent of**  
299 **participants, research interventions or procedures that offer no potential benefits must**  
300 **pose no more than minimal risks. However, a research ethics committee may permit a**  
301 **minor increase above minimal risk when it is not possible to gather the necessary data**  
302 **in another population or in a less risky or burdensome manner, and the social value of**  
303 **the research is compelling (see Guidelines 16 and 17).**
- 304
- 305 • **The aggregate risks of all research interventions or procedures in a study must be**  
306 **considered appropriate in light of the potential benefits to participants and the social**  
307 **value of the research.**
- 308

309 **The researcher, sponsor and research ethics committee must also consider risks to groups**  
310 **and populations, including strategies to minimize these risks.**  
311

#### 312 *Commentary on guideline 4*

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

478

479 *Minimizing risks to groups.* Participation in certain research projects (such as HIV or abortion studies)  
480 may impose upon the research subjects significant risks of social discrimination or harm; such risks  
481 merit consideration equal to that given to adverse medical consequences of experimental drugs and  
482 vaccines. Efforts must be made to reduce their likelihood and severity. For example, participants in  
483 vaccine trials must be enabled to demonstrate that their HIV-seropositivity is most likely due to their  
484 having been vaccinated rather than to natural infection. This may be accomplished by providing them  
485 with documents attesting to their participation in vaccine trials, or by maintaining a confidential  
486 register of trial participants, from which information can be made available to outside agencies at a  
487 participant's request.

488 (See also guidelines 1: *Social value*; 5: *Choice of control*; 10: *Waivers of consent*); 15 *Vulnerable*  
489 *persons*; 16: *Incompetents* 17: *Children*.)

#### 490 **Guideline 5: Choice of control in clinical trials**

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

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

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

- 499 • **there are compelling scientific reasons for using placebo; and**
- 500
- 501 • **delaying or withholding the established effective intervention will result in no more**  
502 **than a minor increase above minimal risk to the participant and risks are minimized,**  
503 **including through the use of effective mitigation procedures.**
- 504

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

#### 507 *Commentary on Guideline 5*

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

517 factors.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

662  
663 Although comparative effectiveness research does not typically delay or withhold an established  
664 effective intervention from participants, the risks associated with the different arms may vary  
665 substantially, for instance when surgical and medical treatment options are being compared. The risks  
666 of standard of care procedures do not necessarily qualify as minimal simply because a treatment has  
667 become standard practice. The risks to participants must be minimized and appropriately balanced in  
668 relation to the prospect of individual benefit or the social value of the research (see guideline 4).  
669

670  
671 **Guideline 6: Caring for participants' health needs**  
672

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

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

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

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

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

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



700

701 *Commentary on guideline 6*

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

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

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

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

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

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

756

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

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

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

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

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

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

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

791 **Guideline 7: Community engagement**

792

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

797

798 *Commentary on guideline 7*

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

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

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

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

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

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

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

867

#### 868 **Guideline 8: Collaborative partnership and capacity building for research and review**

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

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

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

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

889

890 *Commentary on Guideline 8*

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

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

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

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

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

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

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

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

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

935

936 **Guideline 9: Individual informed consent**

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

941 **Researchers have a duty to:**

- 942 • **seek and obtain consent, but only after providing relevant information about the research**  
943 **and ascertaining that the potential participant has adequate understanding of the material**  
944 **facts; and**
- 945 • **refrain from unjustified deception or withholding of relevant information, undue influence,**  
946 **or coercion; and**
- 947 • **ensure that the potential participant has been given sufficient opportunity to consider**  
948 **whether to participate; and**
- 949 • **as a general rule, obtain from each potential participant a signed form as evidence of**  
950 **informed consent. Researchers must justify any exceptions to this general rule and obtain**  
951 **the approval of the research ethics committee.**

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



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

959 *Commentary on Guideline 9*

960

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

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

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

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

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

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

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

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

999 approve a waiver of the requirement of a signed consent under certain conditions (see guideline 4 on  
1000 modifications and waivers of informed consent). Such waivers may also be approved when existence  
1001 of a signed consent form might pose a risk to the participant, for example in studies involving illegal  
1002 behavior. In some cases, particularly when the information is complicated, it is advisable to give  
1003 participants information sheets to retain; these may resemble consent forms in all respects except that  
1004 participants are not required to sign them. Their wording must be approved by the research ethics  
1005 committee. When consent has been obtained orally, researchers are responsible for providing  
1006 documentation of consent to the research ethics committee.

1007 *Renewing consent.* When substantive changes occur in any aspect of a study, the researcher must  
1008 again seek informed consent from the participants. For example, new information may have come to  
1009 light, either from the study itself or other sources, about the risks or benefits of products being tested  
1010 or about alternatives to them. Participants must be given such information promptly. In most clinical  
1011 trials, interim results are not disclosed to researchers or participants until the study has been  
1012 concluded. In long-term studies, the willingness of each participant to continue in the study must be  
1013 ensured.

1014 *Individual informed consent and access to research populations.* In some circumstances a researcher  
1015 may enter a community or institution to conduct research or approach potential participants for their  
1016 individual consent only after obtaining permission from an institution such as school or a prison, or  
1017 after permission from a community leader, a council of elders, or another designated authority. Such  
1018 institutional procedures or cultural customs must be respected. In no case, however, may the  
1019 permission of a community leader or other authority substitute for individual informed consent. In  
1020 some populations, the use of local languages may facilitate the communication of information to  
1021 potential participants and the ability of a researcher to ensure that individuals truly understand the  
1022 material facts. Many people in all cultures are unfamiliar with, or do not readily understand, scientific  
1023 concepts such as placebo or randomization. Sponsors and researchers must develop culturally  
1024 appropriate ways to communicate information necessary for adherence to the standard required in the  
1025 informed consent process. Also, they must describe and justify in the research protocol the procedure  
1026 they plan to use in communicating information to participants. For research conducted in multicultural  
1027 settings, the project must include any resources needed to ensure that informed consent can be  
1028 properly obtained in different linguistic and cultural settings.

1029 *Voluntariness and undue influence.* Informed consent is voluntary if the decision to participate in  
1030 research was made free from undue influence. A variety of influences may affect the voluntariness  
1031 with which consent is provided. Some of these influences can be internal to participants, such as  
1032 mental illness, whereas other influences can be external, such as a dependent relationship between  
1033 participants and clinician-researchers. Circumstances such as severe illness or poverty may threaten  
1034 voluntariness, but do not necessarily imply that participants cannot give voluntary informed consent in  
1035 these situations. Research ethics committees must determine for each individual protocol if influences  
1036 on voluntary consent cross the threshold of becoming undue, and which safeguards are appropriate.

1037

1038 *Dependent relationship.* There are different forms of dependent relationships, such as those between  
1039 teachers and students, and guards and prisoners. In the context of clinical research dependent  
1040 relationships can result from pre-existing relationships between a treating physician and a patient,  
1041 who becomes a potential participant when his or her treating physician takes the role of a researcher.  
1042 The dependent relationship between patients and clinician-researchers may compromise the  
1043 voluntariness of informed consent, since potential participants who are patients depend for medical  
1044 care upon the clinician-researcher and may be reluctant to refuse an invitation to enroll in research in  
1045 which the treating clinician is involved. In some situations of dependency it is considered preferable

1046 that the clinician provide the patient with information since she is most knowledgeable about the  
1047 condition of the patient. However, to minimize the influence of the dependent relationship, several  
1048 protective measures must be taken. Treating clinicians who act as researchers must acknowledge and  
1049 inform patients that they have a double role of the treating clinician and researcher. They must  
1050 emphasize the voluntary nature of participation and the right to withdraw. They must also assure  
1051 patients that their decision whether to participate or to refuse participation will not affect the  
1052 therapeutic relationship or other benefits to which they are entitled. In cases where it is necessary for  
1053 the treating clinician to explain the details of the study protocol, the research ethics committee must  
1054 consider whether the informed consent document must be signed in the presence of a neutral third  
1055 party such as a sufficiently independent nurse or an equally qualified colleague.

1056 *Risks.* Researchers must be completely objective in discussing the details of the experimental  
1057 intervention, the pain and discomfort that it may entail, and known risks and possible hazards. In  
1058 some types of prevention research, potential participants must receive counseling about risks of  
1059 acquiring a disease and steps they can take to reduce those risks. This is especially true of research  
1060 on communicable disease, such as HIV/AIDS prevention research.

1061 *Who obtains consent.* Informed consent must be obtained by a member of the research team.  
1062 Delegation of obtaining consent, for instance to a research nurse or another member of the research  
1063 team, is allowed as long as the person who obtains consent is qualified to obtain consent and has  
1064 prior experience in obtaining consent. The principal researcher is responsible for ensuring that all  
1065 personnel working on the project comply with this guideline.

1066 *Length of the information leaflet.* Information leaflets must be short and preferably not exceed two or  
1067 three pages. The information must be clear and readable and presented using any evidence-based  
1068 methods. Someone with basic education must be able to understand the leaflet. When the informed  
1069 consent document is too long, there must be a short summary. In particular, information on risks that  
1070 are not specific for a study, but are part of the regular treatment, must be avoided. These risks may be  
1071 described in an additional leaflet with information on the standard treatment for a given condition.

1072 *Special considerations regarding informed consent for the use of data in health registries.* The  
1073 requirement to obtain informed consent for research on data in health-related registries may be  
1074 waived, provided the conditions in guideline 10 are met. When a researcher does plan to contact  
1075 persons based on their inclusion in a health-related registry, the researcher must bear in mind that  
1076 these persons may be unaware that their data were submitted to the registry or unfamiliar with the  
1077 process by which researchers obtain access to the data (confer guideline 12). If researchers want to  
1078 contact persons included in a health registry to obtain additional information from them for new  
1079 research, such studies require informed consent.

1080  
1081

## 1082 **Guideline 10: Modifications and waivers of informed consent**

1083 **Researchers must not initiate research involving humans without obtaining each participant's**  
1084 **individual informed consent or that of a legally authorized representative, unless researchers**  
1085 **have received explicit approval to do so from a research ethics committee. In such cases,**  
1086 **before granting a waiver of consent, researchers and research ethics committees must first**  
1087 **seek to establish whether informed consent could be modified in a way that would preserve**  
1088 **the participant's ability to understand the general nature of the investigation and to decide**  
1089 **whether to participate.**

1090 **A research ethics committee may approve a modification or waiver of informed consent to**  
1091 **research if**

- 1092       • **the research would not be feasible or practicable to carry out without the waiver or**  
1093       **modification; and**  
1094       • **the research has important social value; and**  
1095       • **the research poses no more than minimal risks to participants when research**  
1096       **interventions or procedures offer participants no potential benefits.**

1097 **Additional provisions may apply when waivers or modifications of informed consent are**  
1098 **approved in specific research contexts.**

1099

1100 *Commentary on guideline 10*

1101 *General considerations.* A modification of informed consent involves making changes to the informed  
1102 consent process, most frequently in relation to the provision of relevant information and the  
1103 documentation of the participant's informed consent. A waiver of consent allows researchers to  
1104 conduct studies without obtaining informed consent.

1105

1106 As stated in Guideline 9, individuals must be given the opportunity to provide informed consent for all  
1107 health-related research involving humans. Modifications or waivers of informed consent require  
1108 justification and approval. In general, researchers and research ethics committees must seek to  
1109 preserve as much of the informed consent process as possible. They must carefully consider whether  
1110 a modification of the informed consent process would still enable participants to understand the  
1111 general nature of a study and to make a meaningfully informed decision regarding whether or not to  
1112 participate. For instance, in some cases it may be possible to disclose the purpose of a study without  
1113 explicitly informing potential participants of the procedures in the trial arms. Waivers must be granted  
1114 only in cases where a modification of the informed consent process is not possible, or would not offer  
1115 participants sufficient information to make a meaningful decision about participation.

1116 *Modifying the informed consent process by withholding information in order to maintain the scientific*  
1117 *validity of the research.* It is sometimes necessary to withhold information in the consent process to  
1118 ensure the validity of the research. In biomedical research, this typically involves withholding  
1119 information about the purpose of specific procedures. For example, participants in clinical trials are  
1120 often not told the purpose of tests performed to monitor their compliance with the regimen, since if  
1121 they knew their compliance was being monitored they might modify their behaviour and hence  
1122 invalidate results. In most such cases, the potential participants must be asked to consent to remain  
1123 uninformed of the purpose of some procedures until the research is completed. After the conclusion of  
1124 the study they have to be given the omitted information. In other cases, because a request for  
1125 permission to withhold some information would jeopardize the validity of the research, participants  
1126 cannot be told that some information has been withheld until the data has been collected. Any such  
1127 procedure must receive the explicit approval of the research ethics committee. Moreover, before study  
1128 results are analyzed, participants must receive a letter disclosing the information that was withheld  
1129 and giving them the possibility to withdraw their data collected under the study.

1130 *Modifying the informed consent process by actively deceiving participants.* Active deception of  
1131 participants is considerably more controversial than simply withholding certain information. However,  
1132 social and behavioral scientists sometimes deliberately misinform participants to study their attitudes  
1133 and behavior. For example, researchers use "pseudo- patients" or "mystery clients" to study the  
1134 behavior of health-care professionals in their natural settings.

1135 Some people maintain that active deception is never permissible. Others would permit it in certain  
1136 circumstances. Deception is not permissible in cases in which its use would expose participants to  
1137 more than minimal risk. When deception is deemed indispensable to the methods of a study,

1138 researchers must convince the research ethics committee that no other method could obtain valid and  
1139 reliable data; that the research has significant social value; and that no information has been withheld  
1140 that, if divulged, would cause a reasonable person to refuse to participate. Researchers and research  
1141 ethics committees must be aware that deceiving research participants may wrong them as well as  
1142 harm them; participants may resent not having been informed when they learn that they have  
1143 participated in a study under false pretenses. Whenever this is necessary to maintain the scientific  
1144 validity of the research, potential participants must be asked to agree to receiving incomplete  
1145 information during the informed consent process (i.e., researchers obtain consent in advance for the  
1146 deception). The research ethics committee must determine how deceived participants must be  
1147 informed of the deception upon completion of the research. Such informing, commonly called  
1148 "debriefing", ordinarily entails explaining the reasons for the deception. Debriefing is an essential part  
1149 of trying to rectify the wrong of deception. Participants who disapprove of having been deceived for  
1150 research purposes must be offered an opportunity to refuse to allow the researcher to use their  
1151 information obtained through deception. In exceptional cases, a research ethics committee may  
1152 approve the retention of non-identifiable information. For example, an option to withdraw data may not  
1153 be offered in cases where research is evaluating quality of services or competence of providers (for  
1154 example mystery shoppers studies).

1155 *Waiving informed consent.* A research ethics committee may waive informed consent if it is convinced  
1156 by the protocol that the research would not be feasible or practicable to carry out without the waiver;  
1157 and the research has important social value; and the research poses no more than minimal risks to  
1158 participants. These three conditions must also be met even when a study involves personally  
1159 identifiable data or biological specimens, meaning that the data or specimens carry a person's name  
1160 or are linked by a code to a person. The conditions must also be met when studies analyze existing  
1161 data from health-related registries.

1162  
1163 In addition, the three conditions for waiving informed consent must be met when data or biological  
1164 specimens are not personally identifiable and the research has important social value. In this situation,  
1165 the individuals concerned are unknown to the researcher and hence cannot be contacted to obtain  
1166 informed consent. Moreover, because the data or specimens are not personally identifiable, the risks  
1167 to those individuals are no greater than minimal.

1168  
1169 *Special considerations for waiving informed consent in studies performed on health-registry data.*  
1170 The creation and maintenance of health-related registries (for example, cancer registries, databanks  
1171 of genetic and other anomalies in newborn babies) provide a major resource for many public health  
1172 and epidemiological research activities relevant to issues ranging from disease prevention to resource  
1173 allocation. Several considerations support the common practice of requiring that all practitioners  
1174 submit relevant data to such registries: the importance of having comprehensive and accurate  
1175 information about an entire population; the scientific need to include all cases in order to avoid  
1176 undetectable selection bias; and the ethical principle that burdens and benefits must be distributed  
1177 equitably across the population. Hence, registries that are established as mandatory by governmental  
1178 authorities usually involve obligatory rather than voluntary collection of data.

1179  
1180 When a prospective study is performed under a public health mandate or by public health authorities,  
1181 such as disease surveillance, normally neither ethical review nor a waiver of consent is needed  
1182 because the activity is mandated by law. Although the extent and limits of data collection are  
1183 determined by law, researchers must still consider whether, in a given case, it is ethical to use their  
1184 authority to access personal data for research purposes. When the use of such data does not  
1185 constitute (or no longer clearly constitutes) a public health activity, the researcher must seek individual  
1186 consent for the use of the data or demonstrate that the research meets the conditions for waiving  
1187 informed consent, as set out in this guideline. Research projects using data from one or more

1188 mandatory population-based registries should be submitted to a research ethics committee except for  
1189 data analyses inherent to internal institutional activity of a registry.  
1190 *Modified informed consent and broad informed consent.* Also in biobank research individual informed  
1191 consent is modified. Yet the term used for those types of consent is *broad* informed consent. The  
1192 conditions for broad informed consent are discussed in guideline 11.  
1193 (See also guideline 11 on the use of stored materials)  
1194

1193 **Guideline 11: Use of stored biological materials and related data**  
1194 **When biological materials and related data, such as health or employment records, are stored**  
1195 **institutions must have a mechanism to obtain authorization for future use of these materials in**  
1196 **research.**

1197 **When specimens are collected for research purposes, either specific informed consent for a**  
1198 **particular use or broad informed consent for unspecified future use must be obtained from the**  
1199 **source. Such broad informed consent relies on proper governance and management of the**  
1200 **biobank. These types of consent must be obtained in the same way as described in guideline9.**  
1201 **When human biological materials are left over after clinical diagnosis or treatment (so-called**  
1202 **residual tissue) and are stored for future research, a specific or broad informed consent may**  
1203 **be used or may be substituted by an informed opt-out procedure. This means that the material**  
1204 **is stored and used for research unless the person from whom it originates explicitly objects.**  
1205 **The informed opt-out procedure has to fulfill the following conditions: 1) patients need to be**  
1206 **aware of its existence; 2) sufficient information needs to be provided; 3) patients need to be**  
1207 **told that they can withdraw their data; and 4) a genuine possibility to object has to be offered.**

1208 **When researchers seek to use stored materials collected for past research, clinical or other**  
1209 **purposes without having obtained informed consent for their future use for research, the**  
1210 **research ethics committee may waive consent if: 1) the research would not be feasible or**  
1211 **practicable to carry out without the waiver; and 2) the research has important social value; and**  
1212 **3) the research poses no more than minimal risks to participants when research interventions**  
1213 **or procedures offer participants no potential benefits.**

1214 **When researchers use coded material that is stored in a biobank the key to the code must**  
1215 **remain with the custodian of the biobank.**

1216 **Biobanks can only collect biological materials and related data from low resource settings in**  
1217 **collaboration with local health authorities. The governance structure of such biobanks must**  
1218 **have representation of the original setting. If the specimen and data are stored outside the**  
1219 **original setting, there must be provisions to return all materials to the setting concerned and**  
1220 **share possible results and benefits (see guidelines 3, 7 and 8).**

1221 *Commentary on guideline 11*

1222 *General considerations.* The value of repositories for longitudinal studies of specific diseases is widely  
1223 recognized. For this purpose, large population biobanks have been established to allow studies  
1224 across many diseases through correlations of genetic, environmental, occupational, and other health  
1225 data. The vast majority of people do not object to their materials—for example, bodily fluids, cells, or  
1226 tissues—and related data being stored in repositories and used for research for the common good.  
1227 However, the persons whose materials are stored (i.e. the donor) must explicitly authorize this  
1228 undefined future use. Since it is impossible to obtain specific informed consent at the time the material  
1229 is collected, because the precise nature of the research is typically unknown, an acceptable  
1230 alternative to specific informed consent for future research use is broad informed consent. Such broad  
1231 informed consent relies on proper governance and management of the biobank.

1232 *Governance.* Institutions in which biological material and related data are archived after collection for  
1233 research purposes or as “left-over” from clinical diagnosis or treatment must have a governance  
1234 structure in place in which at least the following items are addressed:

- 1235
- 1236 • to which legal entity the material is entrusted;
  - 1237 • how authorization from the patient is obtained;
  - how the donor can retract this authorization;

- 1238 • in which circumstances donors need to be recontacted;
- 1239 • a procedure for determining whether unsolicited findings should be disclosed, and if so, how
- 1240 they should be managed;
- 1241 • how the quality of the material is controlled, ensuring the physical protection and maintenance
- 1242 of the materials;
- 1243 • how confidentiality of the link between biological specimens and personal identifiers of the
- 1244 donors is maintained;
- 1245 • who may have access to the materials for future research, and under which circumstances;
- 1246 • which body may review research proposals for future use of the material;
- 1247 • how participatory engagement with patient groups or the wider community is organized;
- 1248 • to which other sources of personal information the results of analyses on biological materials
- 1249 may be linked;
- 1250 • In broad terms which types of research will be pursued;
- 1251 • which types of research will be in any case excluded or included only after recontacting the
- 1252 donor for consent;
- 1253 • to whom the benefits, material and immaterial, from the research are expected to accrue.

1254 *Research ethics committees and biobanks.* The protocol for every study using stored human biological  
 1255 materials and related data must be submitted to a research ethics committee, which must ensure that  
 1256 the proposed use of the materials falls within the scope agreed to by the donor if he or she has given  
 1257 specific or broad informed consent for future research. If the proposed use falls outside the authorized  
 1258 scope of research, re-consent is necessary. Research ethics committees may waive consent for  
 1259 research with historical materials provided the above three conditions mentioned in the bold text of  
 1260 this guideline are met (see also guideline 10 on modifications and waivers of informed consent).

1261

1262 *Specific informed consent.* When the specific use in research of the collected materials is known at  
 1263 the time of collection, specific informed consent must be obtained as described in guideline 9.  
 1264 Persons who were incompetent at the time their bodily material was stored must be given the  
 1265 opportunity to give informed consent or refusal when they become competent (see guideline 16).

1266

1267 *Broad informed consent.* Broad informed consent describes the range of future uses in research for  
 1268 which consent is given. This broad informed consent should specify: the conditions and duration of  
 1269 storage; who will manage access to the materials; the foreseeable uses of the materials, whether  
 1270 limited to an already fully defined study or extending to a number of wholly or partially undefined  
 1271 studies; and the intended goal of such use, whether only for research, basic or applied, or also for  
 1272 commercial purposes, and the possibility of unsolicited findings and how they will be dealt with. The  
 1273 research ethics committee must ensure that the proposed collections, the storage protocol, and the  
 1274 consent procedure meet these specifications.

1275

1276 *Informed opt-out procedure for research on residual tissue.* Given that human biological materials left  
 1277 over after clinical diagnosis or treatment (so-called residual tissue) are frequently of interest to future  
 1278 researchers, it is good clinical practice to offer donors several options: to have their materials used  
 1279 only for their own treatment or benefit and then discarded; to allow stored materials to be used for a  
 1280 specifically described research project (specific informed consent); or to allow stored materials to be  
 1281 used for yet undefined research, with or without personal identifiers. However, this practice can be  
 1282 difficult to implement, and, an informed opt-out procedure may therefore be acceptable. This implies  
 1283 the material is stored and used for research unless the person from whom it originates explicitly  
 1284 objects.

1285



1286 The informed opt-out procedure has to fulfill the following conditions: 1) patients need to be aware of  
1287 its existence; 2) sufficient information needs to be provided; and 3) patients need to be informed that  
1288 they can withdraw their data; and 4) a genuine possibility to object has to be offered.

1289  
1290 An informed opt-out procedure for research on residual tissue may not be appropriate in certain  
1291 circumstances, namely a) when it involves more than minimal risks to the patient, or b) when  
1292 controversial or high impact techniques are used, for example the creation of immortal cell lines, or c)  
1293 when research is conducted on sensitive tissue types, for example gametes, or d) when research is  
1294 conducted in contexts of heightened vulnerability, for example certain psychiatric patients. A research  
1295 ethics committee must determine whether explicit informed consent for the research is required.

1296 *Authorization for research with archived materials.* When existing repositories of biological materials  
1297 and data collected and stored in the past without explicit informed consent offer important and  
1298 otherwise unobtainable data, a research ethics committee needs to decide whether the use of such  
1299 materials is justified in the absence of explicit consent. The most common justification for using  
1300 records or materials collected in the past without consent is that it would be impracticable or  
1301 prohibitively expensive to locate the persons whose materials or records are to be examined; this may  
1302 happen when, for instance, the study involves reviewing hospital records or performing new tests on  
1303 blood materials collected at a time when consent to future research uses of such materials was not  
1304 usually sought. In addition the research must have important social value; and the research must pose  
1305 no more than minimal risks to participants when research interventions or procedures offer  
1306 participants no potential benefits.

1307 *Anonymization or coding.* Biological material that is stored in biobanks must be anonymised or coded.  
1308 When researchers use coded materials from biobanks in later studies, the key to the code must  
1309 remain with the custodian of the biobank. Thus researchers can only use anonymized or coded  
1310 material.

1311 *Return of results and disclosure of (un)solicited findings.* Especially in the context of repositories  
1312 established for longitudinal study of a particular disease, the informed consent must clearly stipulate  
1313 what return of information—if any—derived from analysis of the materials is foreseen, should the  
1314 participant so wish. There is an emerging consensus that at least some subsets of (genetic) research  
1315 findings must be returned to individual donors if they wish so.

1316 Any disclosure policy of (un)solicited findings must be designed and discussed with the community of  
1317 donors beforehand. Tiered consent, i.e. working with packages or ‘tiers’ of information, gives donors a  
1318 range of choices and allows them to choose some options over others to give them greater control  
1319 over the use of their biological materials. In general, life-saving information and data of immediate  
1320 clinical utility involving a significant health problem must be offered for disclosure, whereas information  
1321 of uncertain scientific validity or meaning would not qualify for communication to the participant.

1322

1323 *Children and adolescents and biobanks.* Children and adolescents who reach the age of maturity  
1324 must be given the opportunity to give broad informed consent to continue the storage and use of their  
1325 collected material and data, and they must at this point also be able to withdraw their consent for  
1326 future research. An informed opt-out system in which persons are explicitly approached and alerted to  
1327 their right to withdraw, could also be acceptable.

1328 *Storing and using material from low-resource settings in biobanks.* Biobanks have become a global  
1329 phenomenon. At the same time, there may be less experience with storing and using biological  
1330 material in some low-resource settings. In addition to what is stated in this guideline, requirements for

1331 community engagement, capacity building and equitable distribution of burdens and benefits of  
1332 research as described in other guidelines also apply to biobank research in low-resource settings (see  
1333 guidelines 3,7,8).

1334 **Guideline 12: Use of health-related data in research**

1335 **When health-related data are stored, institutions must have a mechanism to obtain**  
1336 **authorization for future use of these data in research.**

1337 **If data are collected for research purposes either informed consent for a specific use or broad**  
1338 **informed consent for unspecified future use must be obtained from the source. These types of**  
1339 **informed consent must be obtained in the same way as described in guideline 3.**

1340 **When data are used that were collected in the context of routine clinical care, an informed opt-**  
1341 **out procedure must be used. This means that the data may be stored and used for research**  
1342 **unless a person explicitly objects to this use, such objection being not applicable to data**  
1343 **subject to mandatory inclusion in population-based registries. The informed opt-out procedure**  
1344 **has to fulfill the following conditions: 1) patients need to be aware of its existence; 2) sufficient**  
1345 **information needs to be provided; 3) patients need to be informed that they can withdraw their**  
1346 **data; and 4) a genuine possibility to object has to be offered.**

1347 **When researchers seek to use stored data collected for past research, clinical or other**  
1348 **purposes without informed consent to their use for research, the research ethics committee**  
1349 **may consider waiving the consent of individuals consent if: 1) the research would not be**  
1350 **feasible or practicable to carry out without the waiver; and 2) the research has important social**  
1351 **value; and 3) the research poses no more than minimal risks to participants when research**  
1352 **interventions or procedures offer participants no potential benefits.**

1353 **When researchers use coded health-related data, the key to the code must remain with the**  
1354 **custodian of the biobank.**

1355 **Researchers are only allowed to use anonymized or coded health-related data. The key to the**  
1356 **code must remain with the custodian of the databank.**

1357 **Databanks can only collect data from low resource settings in collaboration with local health**  
1358 **authorities. The governance structure of such a databank must have representation of the**  
1359 **original setting. If the collection is stored outside the original setting there must be provisions**  
1360 **to return all data to the setting concerned and share possible results and benefits.**

1361 *Commentary on guideline 12*

1362 *General considerations.* The value of data collections for longitudinal studies of specific diseases is  
1363 widely recognized. Like with biobanks, a vast majority of people do not object to their data being  
1364 stored in collections and used for research for the common good. Such collections share an important  
1365 characteristic: the persons whose data are stored explicitly agree to this future not yet defined use.  
1366 Therefore it will be impossible to obtain specific informed consent at the time of the collection of the  
1367 data. An acceptable alternative is broad informed consent. Broad informed consent relies on proper  
1368 governance.

1369 *Governance.* Institutions where data are collected and archived must have a governance structure in  
1370 place in which at least the following items are regulated:

- 1371 • to which legal entity the material is entrusted;
- 1372 • how authorization from the donor is obtained;
- 1373 • how the donor can retract this authorization;
- 1374 • in which circumstances donors need to be recontacted;
- 1375 • a procedure for determining whether unsolicited findings should be disclosed, and if so, how
- 1376 they should be managed;
- 1377 • how the quality of the collection is controlled;
- 1378 • how confidentiality of the link between collected data and personal identifiers of the donors is
- 1379 maintained;
- 1380 • who may have access to the data for future research, and under which circumstances;
- 1381 • which body may review research proposals for future use of the data;
- 1382 • how participatory engagement with patient groups or the wider community is organized;

1383

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

- 1384       • In broad terms which types of research will be pursued;  
1385       • which types of research will be in any case excluded or included only after recontacting the  
1386       donor for consent;  
1387       • to whom the benefits, material and immaterial, from the research are expected to accrue.

1388 *Research ethics committees and storing health-related data.* The protocol for every study using  
1389 collected data must be submitted to a research ethics committee, which must ensure that the  
1390 proposed use of the data falls within the scope specifically agreed to by the participant. If not, re-  
1391 consent is necessary.

1392 *Data mining.* Some entities collect data that may be “mined” for health-related research, even if they  
1393 are not collecting health-related data deliberately (for example queries in search engines, consumer  
1394 choices on websites). Such entities must strive for governance structures and mechanisms to obtain  
1395 authorization for future use of these data in research as discussed in this guideline.

1396 *Confidentiality.* An important aspect of storing health-related data is the confidentiality between  
1397 researcher and patient. The collection and storage of information could, if disclosed to third parties,  
1398 cause harm, stigma or distress. Researchers must arrange to protect the confidentiality of such  
1399 information by, for example, by using anonymized or coded data and limiting access to the information  
1400 of third parties. During the process of obtaining informed consent, the researcher must inform the  
1401 potential patients about the safeguards that will be taken to protect confidentiality as well as their  
1402 limitations.

1403 When linked data and materials are used, researchers customarily discard personal identifying  
1404 information when consolidating data for purposes of statistical analysis; this also occurs when  
1405 researchers have linked (or coded) different sets of data regarding individuals with the consent of  
1406 individual participants. When project plans require personal identifiers to remain on records used for a  
1407 study, researchers must explain to research ethics committees why this is necessary and how  
1408 confidentiality will be protected. It can be acceptable to store personally identifiable data to enhance  
1409 their value for future research; by implication, efforts to de-identify data in order to safeguard  
1410 confidentiality and the resulting trade-offs in the scientific value of the given data need to be carefully  
1411 balanced.

1412  
1413 *Limits of confidentiality.* Potential participants must be informed of limits to the ability of researchers to  
1414 ensure strict confidentiality and of the potential adverse consequences of breaches of confidentiality.  
1415 Confidentiality is limited for three reasons. First, even with good governance structures, there is some  
1416 background risk that data are leaked or stolen and thus are obtained by unauthorized third parties.  
1417 Second, data from different sources (for example, health records, employment records, etc.) may be  
1418 linked due to technological advances, which increasingly enables researchers or others to identify  
1419 individuals even when working with anonymized or coded data. Identification is also possible when the  
1420 context in which the research is conducted is narrow (for example small hospital) or very specific (for  
1421 example patients with rare diseases). Pooling data from a number of comparable sources may reduce  
1422 but not completely eliminate the possibility of identifying individuals. In addition, genetic information  
1423 derived through comprehensive technologies (for example whole-genome sequencing) increasingly  
1424 allows identifying individuals. Third, releasing confidential data can be required by law. For example,  
1425 some jurisdictions require the reporting to appropriate agencies of certain communicable diseases or  
1426 evidence of child abuse or neglect. Similarly, (health) authorities and research ethics committee  
1427 accrediting agencies may have the legal right to inspect study records, and a sponsor's compliance  
1428 audit staff may require and obtain access to confidential data. These and similar limits to the ability to  
1429 maintain confidentiality must be anticipated and disclosed to potential participants (see guideline 9,  
1430 individual informed consent).

1431 *Mandatory population-based registries.* Research projects using data from mandatory population-  
1432 based registries must be submitted for review to a research ethics committee except for data analyses  
1433 inherent to the internal institutional research activity of the registry.

1434  
1435 *Specific informed consent* When the specific use in research of the collected data is known at the time  
1436 of collection, specific informed consent must be obtained as described in guideline 9. Persons who  
1437 were incompetent at the time their data was stored must be given the opportunity to give informed  
1438 consent or refusal when they become competent (see guideline 16).

1439  
1440 *Broad informed consent.* Broad informed consent describes the range of future uses in research for  
1441 which consent is given. This broad informed consent should specify: the conditions and duration of  
1442 storage; who will manage access to the data; the foreseeable uses of the data, whether limited to an  
1443 already fully defined study or extending to a number of wholly or partially undefined studies; and the  
1444 intended goal of such use, whether only for research, basic or applied, or also for commercial  
1445 purposes, and, if applicable, the possibility of unsolicited findings and how they will be dealt with. The  
1446 research ethics committee must ensure that the proposed collections, the storage protocol, and the  
1447 consent procedure meet these specifications.

1448  
1449 *Secondary use of stored data.* Sometimes data are collected in databanks, during research or during  
1450 other activities (for example clinical practice, health insurance), that can be used in future research.  
1451 Typically the precise research questions will be unknown at the time of data collection. In those cases  
1452 it is acceptable to use the data for secondary analysis when the intended use falls within the scope of  
1453 the original broad informed consent.

1454 *Archived data* When existing data, collected and stored without an explicit consent process, offer  
1455 important and otherwise unobtainable information, a research ethics committee needs to decide  
1456 whether the use of such data is justified in the absence of explicit consent. The most common  
1457 justification for using data collected in the past without consent is that it would be impracticable or  
1458 prohibitively expensive to locate the persons whose data are to be examined. This may happen when,  
1459 for instance, the study involves reviewing hospital records from a time when consent to future  
1460 research uses of such data was not usually sought. However, data from individuals who have  
1461 specifically rejected such uses in the past may be used only with proper, official authorization in public  
1462 health emergencies.

1463 *Informed opt-out procedure for research with health-related data.* In the absence of broad informed  
1464 consent, an informed opt-out consent procedure can be used. This means that the data is stored and  
1465 used for research unless a person explicitly objects. The informed opt-out procedure has to fulfill the  
1466 following conditions: 1) people need to be aware of its existence; 2) sufficient information needs to be  
1467 provided; 3) a genuine possibility to object has to be offered. However, in certain circumstances the  
1468 researcher must obtain explicit informed consent, whether specific or broad: 1) when the research  
1469 involves higher risks are involved; or 2) when controversial or high impact techniques are used; or 3)  
1470 when the research is conducted with certain vulnerable patients, for example psychiatric patients. A  
1471 research ethics committee must determine whether explicit informed consent is required.

1472  
1473 *Re-contacting participants.* Long term projects often include plans to search for and re-contact  
1474 participants who have been lost to follow-up. Such outreach might also occur when researchers want  
1475 to obtain consent for a new use of stored biological material or data that still has personal identifiers.  
1476 Participants or service users must be made aware of this possibility at the time of initial consent and  
1477 given the choice to opt-out of being re-contacted. Researchers must also establish acceptable  
1478 modalities for establishing contact with those participants or service users who are willing to be  
1479 reached out to for the above-mentioned purposes.

1480 In cases where a researcher does plan to contact persons based on their inclusion in a health-related  
1481 registry, the researcher must bear in mind that these persons may be unaware that their data were  
1482 submitted to the registry or unfamiliar with the process by which researchers obtain access to the data.  
1483 If researchers want to contact persons included in a health registry to obtain additional information from  
1484 them for new research, such studies require individual informed consent (see guideline 9).

1485 *Return of results and (un)solicited findings.* Especially in the context of data collections in which large  
1486 data bases are combined (big data research), the informed consent must clearly stipulate what return  
1487 of information—if any—derived from analysis of the data is foreseen, should the subject so wish. Tiered  
1488 consent--working with packages or 'tiers' of information, gives donors a set of choices and allows  
1489 them to choose some options over others to give them greater control of the use of their data. In  
1490 general, life-saving information and data of immediate clinical utility that entail a significant health  
1491 problem must be offered for disclosure, whereas information of uncertain scientific validity or meaning  
1492 would not qualify for communication to the donor.

1493 *Data-sharing.* Researchers, sponsors and research ethics committees must share data for further  
1494 research where possible. The conditions for data-sharing are spelled out in guideline 24.

1495 *Children and adolescents and collected data.* Children and adolescents who reach the age of maturity  
1496 must be given the opportunity to give broad informed consent to continue the storage and use of their  
1497 collected data and must then also be able to withdraw. An informed opt-out system in which persons  
1498 are explicitly approached and alerted to their right to withdraw, could also be acceptable.

1499 *Storing and using data from low-resource settings in biobanks.* Databanks have become a global  
1500 phenomenon. At the same time, there may be less experience with storing and using data in some  
1501 low-resource settings. In addition to what is stated in this guideline, requirements for community  
1502 engagement, capacity building and equitable distribution of burdens and benefits of research as  
1503 described in other guidelines also apply to databank research in low-resource settings (see guidelines  
1504 3,7,8).



1504 **Guideline 13: Reimbursement and compensation for research participants**

1505 **Research participants must be reasonably reimbursed for direct and indirect expenses**  
1506 **incurred during the research, such as travel costs and lost earnings, and compensated**  
1507 **reasonably for inconvenience and time spent. Compensation can be monetary or non-**  
1508 **monetary. The latter might include free health services unrelated to the research, medical**  
1509 **insurance, educational materials, or other benefits.**

1510 **Compensation must not be so large as to induce potential participants to consent to participate**  
1511 **in the research against their better judgment ("undue inducement"). A local research ethics**  
1512 **committee must approve reimbursement and compensation for research participants.**

1513 **Concerns about undue inducement must not preclude the study of monetary or material**  
1514 **incentives as a potential way of promoting healthy behaviors.**

1515 *Commentary on Guideline 13*

1516 *General considerations.* Participants should not have to pay for making a contribution to the social  
1517 good of research, whether in the form of direct expenses (for example transportation costs) or indirect  
1518 expenses (for example lost earnings), and must therefore be reasonably reimbursed for such  
1519 expenses. In addition, participants must be appropriately compensated for the time spent and other  
1520 inconveniences resulting from study participation. The obligation to reasonably reimburse and  
1521 compensate participants arises even when study enrollment offers participants potential benefits (for  
1522 example investigational drug). This because the vast majority of clinical research studies involve  
1523 research procedures that have no potential benefits for participants but are performed for research  
1524 purposes, such as additional blood draws, extra hospital visits, and overnight stays. Moreover, it  
1525 cannot be known before the research that investigational interventions will benefit participants.  
1526 Indeed, some investigational interventions will prove to cause more harm than good.

1527 *Appropriate compensation.* Participants must also be reasonably compensated for their inconvenience  
1528 and time spent participating in research. Compensation can be monetary or non-monetary and may  
1529 include, for example, health services unrelated to the research, medical insurance, educational  
1530 materials, counseling, or food supplies. Especially when the research poses low risks, providing  
1531 compensation for participating usually does not raise concerns about undue inducement.

1532 *Unacceptable compensation.* Monetary or in kind compensation for research participants must not be  
1533 so large as to persuade them to volunteer against their better judgment or deeply held beliefs (“undue  
1534 inducement”). It can be difficult to evaluate whether an undue inducement exists, in part because the  
1535 compensation that makes someone volunteer against their better judgment depends on their personal  
1536 situation. An unemployed person or a student may view compensation differently from an employed  
1537 person.

1538 Research ethics committees must evaluate monetary and other forms of compensation in light of the  
1539 traditions and socio-economic context of the particular culture and population in which they are  
1540 offered, in order to determine whether the average participant expected to enroll in the study is likely  
1541 to participate in the research against their better judgment because of the compensation offered.  
1542 Consultation with the local community may help to ascertain this. Especially as the risks of research  
1543 procedures that have no potential benefits for participants increase, so does the concern that  
1544 compensation may constitute an undue inducement.

1545 *Compensation for incompetent persons.* Incompetent persons may be vulnerable to exploitation for  
1546 financial gain by their guardians. A guardian asked to give permission on behalf of an incompetent  
1547 person must be offered no compensation other than reimbursement for travel and other direct or  
1548 indirect expenses. Where it would be reasonable to provide compensation to the participants  
1549 themselves, their lack of decisional capacity must not preclude researchers from doing so. When  
1550 participants are incompetent, compensation must be given in a way that participants themselves can  
1551 benefit from it, not the guardians.

1552 *Compensation after study withdrawal.* When a researcher withdraws a participant from a study on  
1553 health-related grounds, the person must be compensated as if full study participation had taken place.  
1554 If the withdrawal is due to a research-related harm, this harm must be treated and the participant is  
1555 entitled to additional compensation as set out in guideline 14. When researchers must withdraw a  
1556 participant from the study for willful noncompliance, they are entitled to withhold part or all of the  
1557 payment. Participants who do not continue study participation for other reasons must be compensated

1558 in proportion to the amount of participation they completed. Researchers must not withhold *all* of the  
1559 monetary compensation until the end of studies involving more than one session or intervention in  
1560 order to induce unwilling participants to remain in the study. The conditions for compensation must be  
1561 approved by the research ethics committee and disclosed during the informed consent process.

1562

1563 *Studies of financial incentives.* In some studies, monetary or material incentives to participants are  
1564 themselves a core object of study, rather than a form of compensation. For example, incentives in the  
1565 form of cash transfers or vouchers might be tested as a means of overcoming economic obstacles to  
1566 treatment (for example to accessing healthcare and continuing treatment) or a lack of effective  
1567 motivation for treatment (for example in long-term treatment for some chronic conditions). Concerns  
1568 about undue inducement must not preclude the conduct of such research, but research ethics  
1569 committees must be sensitive to risks that might emerge for research using incentives.

1570 See also guideline 9: *individual informed consent* and guideline 25: *conflicts of interest*.

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#### 1574 **Guideline 14: Treatment and compensation for research-related harms**

1575 **Sponsors and researchers must ensure that research participants who suffer physical,**  
1576 **psychological or social harm as a result of participating in health-related research receive free**  
1577 **treatment and rehabilitation for such harms, as well as compensation for lost wages, as**  
1578 **appropriate. Such treatment and compensation is owed to research participants who are**  
1579 **harmed, physically, psychologically or socially, as a consequence of interventions performed**  
1580 **solely to accomplish the purposes of research, regardless of fault. In the case of death as a**  
1581 **result of research participation, the participant's dependents are entitled to compensation.**  
1582 **Participants must not be asked to waive the right to free treatment and compensation for**  
1583 **research-related harms.**

1584 **Research ethics committees must evaluate whether there is an adequate arrangement for**  
1585 **treatment and compensation for injuries.**

1586 *Commentary on Guideline 14*

1587 *General considerations.* This guideline focuses on the entitlement to free treatment and additional  
1588 compensation when research participants are harmed by research interventions or procedures. In the  
1589 commentary below the thresholds for such entitlements are described. In that context there is also an  
1590 entitlement of dependents to material compensation for death or disability occurring as a direct result  
1591 of study participation. Not having a proper mechanism in place for compensation of research harms  
1592 may serve as a disincentive for people to participate in research, and may negatively impact trust in  
1593 the research enterprise. Therefore it is not only just, but also pragmatic to have appropriate provision  
1594 for free treatment and compensation for research-related harms.

1595 *Obligation of the sponsor with regard to free treatment and rehabilitation.* Sponsors and researchers  
1596 must ensure that research participants who suffer physical, psychological or social harm as a result of  
1597 participating in health-related research receive free treatment and rehabilitation for such harms. This

1598 will usually mean that in one way or another continuity of care for participants' health needs is  
1599 guaranteed without any cost to the participant for as long as such care is needed (confer Guideline 6).  
1600 This treatment or rehabilitation must be provided for free, since the harm resulted from the research.

1601 *Obligation of the sponsor with regard to compensation.* Before the research begins, the sponsor,  
1602 whether a pharmaceutical company, other organization or institution, or a government (where  
1603 government insurance is not precluded by law), must agree to provide compensation for any harm for  
1604 which participants are entitled to compensation based on this guideline, or come to an agreement with  
1605 the researcher concerning the circumstances in which the researcher must rely on his or her own  
1606 insurance coverage (for example, for negligence or failure of the researcher to follow the protocol, or  
1607 where government insurance coverage is limited to negligence). In certain circumstances it may be  
1608 advisable to follow both courses. Sponsors must seek adequate insurance against risks to cover  
1609 compensation, independent of proof of fault.

1610 *Equitable compensation and free medical treatment.* Compensation is owed to research participants  
1611 who are harmed, psychologically, physically or socially, as a consequence of interventions performed  
1612 solely to accomplish the purposes of research. A harm can be considered a consequence of the  
1613 intervention when the harm would not have happened but for the person's participation in research  
1614 and is different in kind or magnitude from the sorts of harms that would have been reasonable for that  
1615 participant to expect had he or she just received clinical care (for participants who are also patients,  
1616 rather than healthy participants). Compensation must be equitable: researchers and sponsors do not  
1617 have an obligation to pay for care for *any* harm that befalls a participant while in a study. The amount  
1618 of compensation must also be based on pre-specified models of calculation, which must be made  
1619 available by regulatory bodies and is usually based on national jurisprudence. The research ethics  
1620 committee must be satisfied that there is an adequate arrangement for treatment and compensation  
1621 for research-related harms and provide oversight that researchers report on such harms, how  
1622 treatment is being paid for and compensation is provided to participants, and what is being offered.

1623 Participants must not be asked to waive their rights to free treatment or compensation for research-  
1624 related harms, nor must they be required to show negligence or lack of a reasonable degree of skill on  
1625 the part of the researcher in order to claim free treatment or compensation. The informed consent  
1626 process or form must contain no words that would absolve an researcher from responsibility in the  
1627 case of harm, or that would imply that participants would waive their right to seek compensation (see  
1628 guideline 9). Prospective participants must be informed that they will not need to take legal action to  
1629 secure the free treatment or compensation for harm to which they may be entitled. They must also be  
1630 told what medical service or organization or individual will provide the treatment and what organization  
1631 will be responsible for providing compensation.

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## 1636 **Guideline 15: Research involving vulnerable persons**

1637 **When vulnerable individuals and groups are considered for recruitment in research,**  
1638 **researchers and research ethics committees must ensure that specific protections are in place**

1639 **to safeguard the rights and welfare of these individuals and groups in the conduct of the**  
1640 **research.**

1641 *Commentary on Guideline 15*

1642 *General considerations.* According to the *Declaration of Helsinki*, vulnerable groups and individuals  
1643 “may have an increased likelihood of being wronged or of incurring additional harm.” In some cases,  
1644 persons are vulnerable because they are relatively (or absolutely) incapable of protecting their own  
1645 interests. This may occur when persons have relative or absolute impairments in decisional capacity,  
1646 education, resources, strength, or other attributes needed to protect their own interests. In other  
1647 cases, persons can also be vulnerable because some feature of the circumstances (temporary or  
1648 permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their  
1649 interests. This may happen when people are marginalized, stigmatized, or face social exclusion or  
1650 prejudice that increases the likelihood that others place their interests at risk, whether intentionally or  
1651 unintentionally. Although research ethics committees can require special protections only for groups  
1652 considered for enrolment in a particular project, researchers and others involved in research must  
1653 take into account factors that render individual potential or enrolled participants vulnerable and take  
1654 appropriate steps to mitigate those factors.

1655 A traditional approach to vulnerability in research has been to label entire classes of individuals as  
1656 vulnerable. The account of vulnerability in this guideline seeks to avoid considering entire classes of  
1657 individuals as vulnerable. However, it is useful to look at the specific characteristics that may render  
1658 individuals vulnerable, as it can aid in identifying the special protections needed for persons who may  
1659 have an increased likelihood of being wronged or of incurring additional harm as participants in  
1660 research.

1661 Some characteristics can make it reasonable to assume that certain populations are vulnerable, for  
1662 example:

1663 *Capacity to consent.* One widely accepted criterion of vulnerability is limited capacity to consent or  
1664 decline to consent to research participation. Individuals with this characteristic are discussed in other  
1665 guidelines in this document (Guidelines 16: persons who are incapable of giving informed consent and  
1666 17: Children and adolescents)

1667 *Individuals in hierarchical relationships.* The characteristic of vulnerability in this case is the possibility  
1668 of diminished voluntariness of the consent of potential participants who are in a subordinate  
1669 relationship. Examples are medical and nursing students, subordinate hospital and laboratory  
1670 personnel, employees of pharmaceutical companies, and members of the armed forces or police.  
1671 Their agreement to volunteer may be unduly influenced, whether justified or not, by the expectation of  
1672 preferential treatment if they agree to participate in the study or by fear of disapproval or retaliation if  
1673 they refuse (see also commentary to guideline 9). The research protocol must include a description of  
1674 provisions to protect such individuals from being conscripted into research.

1675 *Institutionalized persons.* Residents of nursing homes, mental institutions, and prisons are often  
1676 considered vulnerable because in a confined setting they have few options and are denied certain  
1677 freedoms that non-institutionalized persons enjoy. For example, prisons have been described as “an  
1678 inherently coercive environment.” Also they may be in a dependent relationship with caregivers or  
1679 guardians (see dependent relationship guideline 9).

1680 One protection for institutionalized individuals is the appointment of an advocate of some sort to the  
1681 research ethics committee when such proposals are under review (confer the dependent relationship  
1682 in guideline 9). Some individuals with this characteristic may also have diminished capacity to

1683 consent, and therefore require the additional protections noted earlier for participants who lack  
1684 decisional capacity.

1685 *Women.* Although in general women must not be considered vulnerable, specific circumstances in  
1686 which women may be considered vulnerable in research include: research on intimate partner  
1687 violence; studies of abortion in jurisdictions where abortion is illegal; research with women who live in  
1688 a cultural context where they are not permitted to consent on their own behalf for participation in  
1689 research, but require permission from a spouse or male relative. When women in such situations are  
1690 potential participants in research, researchers need to exercise special care (see guideline 18).

1691 *Pregnant women.* Pregnant women must not be considered vulnerable simply because they are  
1692 pregnant. Specific circumstances, such as risks to the fetus, may require special protections, as set  
1693 out in guideline 19.

1694 *Other potentially vulnerable individuals.* Among members of groups that have traditionally been  
1695 considered vulnerable, the following are frequently mentioned: people receiving welfare benefits or  
1696 social assistance and other poor people and the unemployed; people who perceive participation as  
1697 the only means of accessing medical care; some ethnic and racial minorities; homeless persons,  
1698 nomads, refugees or displaced persons; people living with disabilities; patients with incurable disease;  
1699 individuals who are politically powerless; and members of communities unfamiliar with modern  
1700 medical concepts.

1701 To the extent that these and other people have one or more of the characteristics discussed above,  
1702 research ethics committees must review the need for special protection of their rights and welfare, and  
1703 include such protections when necessary. However, researchers and research ethics committees  
1704 must avoid making judgments regarding the exclusion of such groups based on stereotypes. One  
1705 proposed mechanism that can be used to avoid stereotyping is community consultation, where  
1706 feasible, before and during the conduct of the research (see guideline 7 on community engagement).

1707 *Special protections.* Special protections for these groups can include allowing no more than minimal  
1708 risks for procedures that offer no potential benefits for participants; supplementing the participant's  
1709 agreement by the permission of family members, legal guardians, or other appropriate  
1710 representatives; or requiring that the research be carried out only when it is targeted at conditions that  
1711 affect these groups. Research ethics committees need to be sensitive to not overly excluding people,  
1712 and allow them to participate by specifying special protections.

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#### 1715 **Guideline 16: Research involving individuals who are not capable of giving informed consent**

1716 **Individuals who are not capable of giving informed consent may have distinctive health needs**  
1717 **that require research in this population. At the same time, they may not be able to protect their**  
1718 **own interests due to their lack of capacity to provide informed consent. Specific protections to**  
1719 **safeguard the rights and welfare of these subjects in research are therefore necessary.**

1720 **Before undertaking research with individuals who are incapable of giving informed consent,**  
1721 **the researcher and the research ethics committee must ensure that**

- 1722 • a legally authorized representative of the person who is incapable of giving informed  
1723 consent has given permission and this permission takes account of the participant's  
1724 previously formed preferences and values; *and*
- 1725 • the assent of each subject has been obtained to the extent of that person's capacity,  
1726 after having been provided with adequate information about the research at the level of  
1727 the subject's capacity for understanding this information; *and*
- 1728 • in the case of emergency research, participants have made advance directives, where  
1729 feasible, for participation in research while fully capable of giving informed consent or  
1730 their communities have been engaged.
- 1731 For research interventions or procedures that have the potential to benefit individuals who are  
1732 incapable of giving informed consent, the risks must be minimized and outweighed by the  
1733 prospect of individual benefit.
- 1734 If participants become capable of giving informed consent during the research, their consent  
1735 to continued participation must be obtained.
- 1736 In general, a potential participant's refusal to enroll in the research must be respected, unless,  
1737 in exceptional circumstances, research participation is considered the best available medical  
1738 alternative for the individual who is incapable of giving informed consent.
- 1739 For research interventions or procedures that have no potential benefits for participants, two  
1740 conditions apply:
- 1741 • the risks must be minimized and no more than minimal, *and*

- 1742
- 1743
- 1744
- 1745
- **they must be studied first in persons who can give consent when these interventions and procedures are targeted at conditions that affect persons who are not capable of giving informed consent as well as those who are, unless the necessary data cannot be gathered without participation of persons who are incapable of giving informed consent.**



1746 **When the social value of the studies with such research interventions and procedures is**  
1747 **compelling, and these studies cannot be conducted in persons who can give informed**  
1748 **consent, a research ethics committee may permit a minor increase above minimal risk.**

1749

1750 *Commentary on Guideline 16*

1751 *General considerations.* In general, competence or decisional capacity is determined by the ability to  
1752 understand material information, appreciate the situation and its consequences, reason about the  
1753 treatment options, and communicate a choice. Participants may be incapable to give informed  
1754 consent for a variety of reasons (for example dementia, some psychiatric conditions and accidents).  
1755 Moreover, lack of capacity is time, task and context specific. Persons can become capable of giving  
1756 informed consent after a certain period, or they can be incompetent to decide whether they should be  
1757 treated for a certain disease but competent to decide whether they want to enjoy a meal. In order to  
1758 adequately treat people who suffer from conditions related to their decisional capacity, research with  
1759 incapacitated participants is essential.

1760 When researchers have reason to believe that potential or current participants are incapacitated, the  
1761 participant's decisional capacity must be adequately assessed. In cases where incompetence might  
1762 reasonably be expected, participants must be routinely screened. However, it is important to note that  
1763 diagnosis of a mental or behavioral disorder does not necessarily imply that individuals are incapable  
1764 of giving informed consent.

1765 *Minor increase above minimal risk.* Research risks are minimal when the risk of serious harm is very  
1766 unlikely and the potential harms associated with more common adverse events are low (see guideline  
1767 4). Risks in research must be compared to risks that an average, normal, healthy individual  
1768 experiences in daily life or during routine examinations. If the risks are considered as minimal in these  
1769 situations, they may also be considered as minimal in clinical research (see guideline 4). A research  
1770 ethics committee may permit a minor increase above minimal risk for research interventions and  
1771 procedures that have no potential benefits when the necessary data cannot be gathered in  
1772 incapacitated persons and in a less risky or burdensome manner, and the social value of the research  
1773 is compelling. While there is no precise definition of a "minor increase" above minimal risk, the  
1774 increment in risk must only be a fraction above the minimal risk threshold and considered acceptable  
1775 by a reasonable person.

1776 *Assent and dissent.* If participants cannot consent because they are incapacitated due to mental or  
1777 behavioral disorders, they must be engaged in the research discussion at the level of their capacity to  
1778 understand, and they must be given a fair opportunity to agree to or to decline participation in the  
1779 study. This can also be called obtaining the participant's assent or dissent. Assent and dissent must  
1780 be considered as a process that responds to changes in the person's cognitive status (see guideline  
1781 9).

1782 Absence of affirmative agreement or explicit objection must be respected unless the treating physician  
1783 and representative regard participation in research as the best available medical alternative. Any  
1784 explicit objection by persons who are incapable to give informed consent due to mental or behavioral  
1785 disorders must be respected even if the legally authorized representative has given permission. An  
1786 explicit objection may be overruled if the incapacitated person with the mental or behavioral disorder  
1787 needs treatment that is not available outside the context of research, the research intervention shows  
1788 a clear prospect of clinical benefit (confer guideline 4), and the treating physician and the legally  
1789 authorized representative consider the research intervention to be the best available medical  
1790 alternative for the person lacking capacity.

1791 *Permission of a legally authorized representative.* In accordance with national regulation, the  
1792 permission of an immediate family member or other person with a close personal relationship with the  
1793 individual must be sought. Surrogate decision makers must evaluate to what extent study participation  
1794 is consistent with the individual's preferences and values, and – in the case of research that offers  
1795 participants a prospect of clinical benefit – to what extent study participation promotes the individual's  
1796 clinical interests. Previously stated or documented preferences regarding the individual's willingness  
1797 to enroll in research must be respected. Researchers must recognize that surrogates may have their  
1798 own interests that may call their permission into question.

1799 *Emergency care situations in which the researcher anticipates that many participants will be unable to*  
1800 *consent.* Research protocols are sometimes designed to address conditions occurring suddenly and  
1801 rendering the patients or participants incapable of giving informed consent. Examples are sepsis,  
1802 head trauma, cardiopulmonary arrest and stroke. In such circumstances it is often necessary to  
1803 proceed with the research interventions very soon after the onset of the condition in order to evaluate  
1804 an investigational treatment or develop the desired knowledge.

1805 If possible, an attempt must be made to identify a population that is likely to develop the condition to  
1806 be studied. This can be done readily, for example, if the condition is one that recurs periodically in  
1807 individuals, such as grand mal seizures and alcohol binges. In such cases, researchers should ideally  
1808 contact potential participants while fully capable of informed consent, and obtain their agreement to be  
1809 involved in the research during future periods of incapacitation.

1810 If there is no opportunity to solicit informed consent of participants while fully capable of informed  
1811 consent, plans to conduct emergency care research with incapacitated persons must be publicized  
1812 within the community in which it will be carried out, where feasible. In the design and conduct of the  
1813 research, the research ethics committee, the researchers and the sponsors must be responsive to the  
1814 concerns of the community. If there is cause for concern about the acceptability of the research in the  
1815 community, there must be a formal consultation with representatives designated by the community.  
1816 The research must not be carried out if it does not have substantial support in the community  
1817 concerned. (See guideline 4 commentary, *Risks to groups of persons*, and guideline 7 on Community  
1818 engagement)

1819 Before proceeding without prior informed consent, the researcher must make reasonable efforts to  
1820 locate a legally authorized representative to give permission on behalf of an incapacitated patient in  
1821 need of emergency care. If such a person can be located and refuses to give permission, the patient  
1822 may not be enrolled as a participant. The risks of all interventions and procedures will be justified as  
1823 required by guideline 4. The researcher and the research ethics committee must agree to a maximum  
1824 time of involvement of an individual without obtaining either the individual's own informed consent or  
1825 surrogate consent according to national regulation if the person continues to be unable to give  
1826 consent. If by that time there is no individual or surrogate consent, the participant must be withdrawn  
1827 from the study provided that withdrawal will not make the participant worse off. The participant or the  
1828 surrogate must be offered an opportunity to object to the use of data derived from participation of the  
1829 patient without consent or permission.

1830 When there are no advance directives for research participation for the period of incapacitation,  
1831 permission of a legally authorized representative must be sought. This permission must take account  
1832 of the participant's previously formed preferences and values.

1833 In all cases in which research has been approved to begin without prior consent of incapacitated  
1834 persons because of suddenly occurring conditions, they must be given all relevant information as  
1835 soon as they regain capacity, and their consent to remain in the study must be obtained as soon as is  
1836 reasonably possible. In addition, they must be given the opportunity to opt out from the study.

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1841 **Guideline 17: Research involving children and adolescents**

1842 **Children and adolescents have distinctive physiologies and health needs that require research**  
1843 **in this population. Research designed to obtain knowledge relevant to the health needs of**  
1844 **children and adolescents must therefore be promoted. However, their distinctive physiologies**  
1845 **may also place children and adolescents at increased risk of being harmed in the conduct of**  
1846 **research. Moreover, they may not be able to protect their own interests due their developing**  
1847 **capacity to give informed consent. Specific protections to safeguard children’s rights and**  
1848 **welfare in the research are therefore necessary.**

1849 **Before undertaking research involving children and adolescents, the researcher and the**  
1850 **research ethics committee must ensure that**

- 1851       • **a parent or a legally authorized representative of the child or adolescent has given**  
1852       **permission.**
- 1853
- 1854       • **the agreement (assent) of the child or adolescent has been obtained in keeping with**  
1855       **the child’s/adolescent’s capacity after having been provided with adequate information**  
1856       **about the research tailored to the child’s/adolescent’s maturity.**

1857 **If children reach the legal age of maturity during the research, their consent to continued**  
1858 **participation must be obtained.**

1859 **In general, the refusal of a child or adolescent to participate or continue in the research must**  
1860 **be respected, unless, in exceptional circumstances, research participation is considered the**  
1861 **best medical alternative for the child.**

1862 **For research interventions or procedures that have the potential to benefit children or**  
1863 **adolescents, the risks must be minimized and outweighed by the prospect of individual benefit.**

1864 **For research interventions or procedures that have no potential benefits for participants, two**  
1865 **conditions apply:**

- 1866 • **the risks must be minimized and no more than minimal, *and***
- 1867 • **they must be studied in adults first, when these interventions and procedures are**  
1868 **targeted at conditions that affect adults as well as children and adolescents, unless the**  
1869 **necessary data cannot be gathered without participation of children or adolescents.**

1870 **When the social value of the studies with such research interventions and procedures is**  
1871 **compelling, and these studies cannot be conducted in adults, a research ethics committee**  
1872 **may permit a minor increase above minimal risk.**

1873

1874 *Commentary on Guideline 17*

1875 *Justification of the involvement of children and adolescents in health-related research.* The  
1876 participation of children and adolescents is indispensable for research into diseases of childhood and  
1877 conditions to which they are particularly susceptible, as well as for clinical trials of drugs that will be  
1878 used for children and adolescents as well as adults. In the past, many new products were not tested in  
1879 children or adolescents though they were directed towards diseases also occurring in childhood. In  
1880 some cases this resulted in children being exposed to interventions that were not effective or that  
1881 were harmful. In general, this lack of information results in higher risks for children and adolescents  
1882 from being exposed to interventions where little is known about their specific effects or safety in this  
1883 population. Therefore, it is imperative to involve children and adolescents in research to study both  
1884 investigational interventions for childhood conditions and established interventions in adults that are  
1885 also relevant for children or adolescents, but that have not previously undergone rigorous testing in  
1886 children and adolescents.

1887 *Order of involvement in research.* There is a controversy over whether research must be done first in  
1888 adults or adolescents before it is done in (younger) children. Some think that all studies must be done  
1889 in adults first in order to minimize risks in children. Others argue that this requirement can preclude  
1890 valuable and timely research in children, in particular when the research addresses an important  
1891 health need or priority of children.

1892

1893 These guidelines acknowledge the general rationale behind inclusion of adults before children is that  
1894 children must be protected from unnecessary risks of harm. However, a strict adherence to this  
1895 requirement may not always be tenable in pediatric research since children and adolescents face  
1896 distinctive health problems. In the case of childhood specific conditions, studies in adults would not be  
1897 feasible nor their results meaningful. Moreover, in rare cases (for example when a disease affects  
1898 large numbers of people, including children and adolescents, the available treatment options are  
1899 limited, and an investigational agent shows great promise), waiting for conclusive results from  
1900 research in adults before initiating pediatric studies can significantly delay the development of  
1901 beneficial interventions.

1902

1903 The current guidelines do not require that research first be conducted in adults if the research includes  
1904 interventions that hold out the prospect for individual benefit for participants. This prospect is sufficient  
1905 to justify the risks associated with the interventions and procedures, provided the cumulative risk of all  
1906 study interventions and procedures that do not hold out the prospect of individual benefit is no more  
1907 than minimal. If research meets these conditions but the cumulative risk of all study interventions and  
1908 procedures that do not hold out the prospect of individual benefit is only a minor increment above

1909 minimal risk, then research ethics committees must be convinced that the research is of special  
1910 relevance to children or adolescents and could not be carried out equally well in an adult population.  
1911 In such cases, older children who are more capable of giving assent must be selected before younger  
1912 children or infants, unless there are sound scientific reasons for performing the research in younger  
1913 children first.

1914  
1915 Research must always be conducted in adults before it is conducted in children if it does not include  
1916 interventions and procedures that hold out the prospect of benefit to participants, as in the case of  
1917 drug toxicity studies. First exploring the toxicity of new drugs in adult populations represents a way of  
1918 reducing risk for children and adolescents who might be involved in subsequent investigations of the  
1919 same intervention.

1920  
1921 *Minimal risk and a minor increase above minimal risk.* Research risks are minimal when the risk of  
1922 serious harm is very unlikely and the potential harms associated with more common adverse events  
1923 are low (see guideline 6). Risks in research must be compared to risks that an average, normal,  
1924 healthy child experiences in daily life or during routine examinations. If the risks are considered as  
1925 minimal in these situations, they may also be considered as minimal in pediatric research (see  
1926 guideline 6). A research ethics committee may permit a minor increase above minimal risk for  
1927 research procedures that have no prospect of benefit when the necessary data cannot be gathered in  
1928 adults and in a less risky or burdensome manner, and the social value of the research for children or  
1929 adolescents is compelling. While there is no precise definition of a "minor increase" above minimal  
1930 risk, the increment in risk must only be a fraction above the minimal risk threshold and considered  
1931 acceptable by a reasonable person (see guideline 4).

1932  
1933 *Assent.* Children and adolescents who are legal minors cannot give legally valid informed consent, but  
1934 they may be able to give assent. To give assent means that the child or adolescent is engaged in the  
1935 research discussion in accordance with his or her capacities. Assent must be considered as a process  
1936 (see guideline 3). Furthermore, the researcher must involve the child or adolescent in the actual  
1937 decision-making process and use age-appropriate information. It is of major importance to inform the  
1938 child or adolescent and obtain assent as described above, preferably in writing when the child  
1939 becomes literate. The process of obtaining assent must take into account not only the age of children,  
1940 but also his or her individual circumstances, life experiences, emotional and psychological maturity,  
1941 intellectual capabilities and the child's or adolescent's family situation.

1942 If child participants reach the legal age of majority and become capable of independent informed  
1943 consent during the research, their informed consent to continued participation must be sought and  
1944 their decision respected.

1945 *Deliberate objection.* Some children and adolescents who are too immature to give assent may be  
1946 able to register a 'deliberate objection', i.e. an expression of disapproval or refusal of a proposed  
1947 procedure. The deliberate objection of an older child or adolescent, for example, is to be distinguished  
1948 from the behaviour of an infant that is likely to cry or withdraw in response to almost any adverse  
1949 stimulus. A deliberate objection by a child or adolescent to taking part in research must be respected  
1950 even if the parents have given permission, unless the child or adolescent needs treatment that is not  
1951 available outside the context of research, the research intervention has a clear prospect of clinical  
1952 benefit, and the treating physician and the legally authorized representative consider the research  
1953 intervention to be the best available medical alternative for the given child or adolescent. In such a  
1954 case, particularly if the child is very young or immature, a parent or guardian may override the child's  
1955 objections. However, in some situations parents may press an researcher to persist with an  
1956 investigational intervention against the child's wishes. Sometimes this pressure is meant to serve the  
1957 parents' interests rather than the child's. In this case, the parents must be overridden if the researcher  
1958 believes it is not in the child's best clinical interest to enroll or continue study participation.

1959

1960 *Permission of a parent or guardian.* The researcher must obtain the permission of at least one parent  
1961 or guardian in writing consistent with applicable laws and regulations. The age at which a child  
1962 becomes legally competent to give consent differs substantially from one jurisdiction to another. Often  
1963 children who have not yet reached the legally established age of consent can understand the  
1964 implications of research participation and go through standard informed consent procedures; however,  
1965 legally they can only assent to serve as research participants. Independent of its quality, assent is  
1966 always insufficient to permit participation in research unless it is supplemented by the permission of a  
1967 parent, a legal guardian or other duly authorized representative. The decision to continue or  
1968 discontinue participation by children or adolescents who become legally competent during the study  
1969 trumps the decision of their parents or legal guardians.

1970 *Waiver of parental permission.* In certain circumstances, research ethics committees may waive  
1971 parental permission. In such cases special protections must be devised to ensure that the best  
1972 interests of these children or adolescents are being served. These circumstances might include cases  
1973 in which permission of a parent is infeasible or undesirable. In some jurisdictions, certain individuals  
1974 who are below the general age of consent are regarded as "emancipated" or "mature" minors and are  
1975 authorized to consent without the agreement or even the awareness of their parents or guardians.  
1976 They may be married, pregnant or be parents themselves, or they may live independently. In other  
1977 cases, studies involve investigation of adolescents' beliefs and behaviour regarding sexuality or use of  
1978 recreational drugs. Research may also address domestic violence, sexually transmitted diseases,  
1979 pregnancy, abortion, or child abuse. In these cases parental knowledge of the subject matter may  
1980 place the children or adolescents at risk of questioning, intimidation, or even physical harm by their  
1981 parents. In still other cases, children or adolescents do not have a legal representative, such as  
1982 orphans.

1983 In such cases, special protections to promote the best interests of these children or adolescents must  
1984 include the involvement of independent child advocates. A child may also be asked to choose a  
1985 relative, trusted friend, or family physician who is not involved in the research project who might then  
1986 represent the child. Independent psychological and medical support for the participating children and  
1987 adolescents is another special protection, though this may be difficult to realize in some communities.  
1988 In such communities the study personnel must be sufficiently qualified to help children and  
1989 adolescents who need medical and psychological support.

1990 *Observation of the study by a parent or guardian.* A parent or guardian who gives permission for a  
1991 child or adolescent to participate in research must generally be given the opportunity, to a reasonable  
1992 extent, to observe the study as it proceeds, so as to be able to withdraw the child if the parent or  
1993 guardian decides it is in the child's best interests to do so.

1994 (See also Guideline 4: *Potential benefits and risks of study participation*; and Guideline 15: *Research*  
1995 *involving vulnerable persons.*)

1992 **Guideline 18: Women as research participants**

1993 **Women have distinctive physiologies and health needs and must be included in biomedical**  
1994 **research unless a good scientific reason justifies their exclusion. In research involving women,**  
1995 **only the informed consent of the woman herself is required for her research participation. In no**  
1996 **case must the permission of another person replace the requirement of individual informed**  
1997 **consent by the woman.**

1998 *Commentary on Guideline 18*

1999 *General considerations.* Women in many societies have been discriminated against with regard to their  
2000 involvement in research. In particular, women who are biologically capable of becoming pregnant have  
2001 been traditionally excluded from clinical trials of drugs, vaccines and medical devices owing to concern  
2002 about undetermined risks to the fetus. Although the presumption against including women has changed  
2003 in recent years, they are still excluded in many cases without adequate justification. Much remains  
2004 unknown about the safety and efficacy of most drugs, vaccines, or devices used by women in medical  
2005 practice, and this lack of knowledge can be dangerous.

2006 *Inclusion of women of childbearing age.* A general policy of excluding from clinical studies women who  
2007 are biologically capable of becoming pregnant is unjust in that it deprives them of the benefits of new  
2008 knowledge derived from these studies. It is also an affront to their right of self-determination. Although  
2009 women of childbearing age must be given the opportunity to participate in research, they must be  
2010 informed that the research could include risks to the fetus if they become pregnant during the research  
2011 (see guideline 15). When participation in research might be hazardous to a fetus or a woman if she  
2012 becomes pregnant, sponsors and researchers must guarantee potential participants access to a  
2013 pregnancy test and to effective contraceptive methods before the research begins. Researchers must  
2014 never recruit women who might become pregnant for research that is known or likely to be hazardous  
2015 when access to contraceptive methods is absent, even if the absence is due to legal or religious  
2016 reasons. For women who are not pregnant at the outset of a study but who might become pregnant  
2017 while they are research participants, the consent discussion must include information about terminating  
2018 the pregnancy, including the circumstances in which abortion is legally permitted in that jurisdiction.  
2019 Also, if the pregnancy is not terminated, participants must be guaranteed a medical follow-up for their  
2020 own health and that of the infant and child.

2021 *Women who become pregnant during research.* Many biomedical protocols call for stopping the  
2022 participation of women who become pregnant during the research. In cases where a drug or biological  
2023 product is known to be mutagenic or teratogenic, women must be removed from the study and access  
2024 to diagnostic tests must be provided to reveal any fetal anomalies. If anomalies are detected, women  
2025 may be referred for an abortion where it is legally available. When there is no evidence on the basis of  
2026 which a potential harm to the fetus can be assumed, women who become pregnant must not  
2027 automatically be removed from the study, but must be offered the option to continue or end their  
2028 participation. In case the women opt for continued participation, researchers and sponsors must offer  
2029 adequate monitoring and support.

2030 *Vulnerability.* Some women become vulnerable in research because of heightened psychological,  
2031 social, physical, or legal risks. Examples include surveys and interviews regarding intimate partner  
2032 violence and rape; social and behavioral research involving sex workers or women who inject drugs;  
2033 and studies that solicit information about sexual behavior. Breach of confidentiality in these types of  
2034 research could result in serious harms to women, even if the only information disclosed is their  
2035 participation in the research.



2036 When women are vulnerable and potential participants in research, researchers need to exercise  
2037 special care in the evaluation of risks and potential benefits as well as the informed consent process. In  
2038 some cultures spouses or community leaders typically grant permission to invite women to participate.  
2039 This authorization must not be used as a substitute for individual informed consent. The women must  
2040 have adequate time and a proper environment in which to decide to enroll. When the research involves  
2041 household surveys or interviews, researchers must take special care to ensure that the women are  
2042 interviewed in a private place without the possibility of intrusion by other family members. In such  
2043 studies, women must be given the option of conducting the interview in a setting of their choosing  
2044 outside the home. In studies involving women who have experienced gender-based violence,  
2045 participation in interviews may cause emotional distress. Researchers must be prepared with referrals  
2046 for psychological counseling if the need arises.

2047

2048

2049

2050 **Guideline 19: Pregnant and lactating women as research participants**

2051 **Pregnant and lactating women have distinctive physiologies and health needs. Research**  
2052 **designed to obtain knowledge relevant to the health needs of the pregnant and lactating woman**  
2053 **must be promoted. Research in pregnant women must be initiated after careful consideration of**  
2054 **the best available relevant data.**

2055

2056 **In no case must the permission of another person replace the requirement of individual**  
2057 **informed consent by the pregnant or lactating woman.**

2058 **For research interventions or procedures that have the potential to benefit either pregnant or**  
2059 **lactating women or their fetus or infant, risks must be minimized and outweighed by the**  
2060 **prospect of individual benefit.**

2061 **For research interventions or procedures that have no potential benefits for participants**

2062 

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

2063 

- **the purpose of the research must be to obtain knowledge relevant to the particular**  
2064 **health needs of pregnant or lactating women or their fetuses or infants.**

2065 

- **When the social value of the research for pregnant or lactating women or their fetus or**  
2066 **infant is compelling, and the research cannot be conducted in non-pregnant or non-**  
2067 **lactating women, a research ethics committee may permit a minor increase above**  
2068 **minimal risk.**

2069 **All research involving pregnant women must include short term and long-term follow up of**  
2070 **future children, as adverse events associated with research in pregnancy may not occur**  
2071 **immediately.**

2072 **As a general rule, health related research involving pregnant women that has the potential for**  
2073 **serious harm to the fetus must be conducted only in settings where women can be guaranteed**  
2074 **access to a safe, timely and legal abortion in the event that participation in the research makes**  
2075 **the pregnancy unwanted**

2076 *Commentary on guideline 19*

2077 *General considerations.* Physicians prescribe medications for pregnant and lactating women, but most  
2078 often do so in the absence of studies involving such women and without adequate evidence of safety  
2079 and efficacy. A direct consequence of the routine exclusion of pregnant women from clinical trials is  
2080 their use of medications (both prescription and non-prescription) lacking data from clinical trials about  
2081 the potential benefits and harms to themselves, their fetuses and their future children. Therefore, it is  
2082 imperative to involve pregnant and lactating women in research to learn about the currently unknown  
2083 risks and benefits to them, as well as to the fetus or nursing infant.

2084  
2085 A case in point is the thalidomide episode, in which about 10,000 babies around the world (many in  
2086 western Europe) were born with severely deformed limbs because their mothers had taken  
2087 medication when pregnant. This tragedy is often cited as a reason for excluding pregnant women from  
2088 biomedical research, but the lesson to be learned is the opposite. Never having been tested in pregnant  
2089 women, the drug came to market and was readily available for morning sickness, a relatively mild  
2090 condition. Had the drug been tested in very few women in a clinical trial, the mutagenic effect would  
2091 most likely have been discovered and the total number of babies born with deformities would have  
2092 been much smaller.

2093  
2094 Research designed to obtain knowledge relevant to the health needs of pregnant and lactating women  
2095 should be promoted in the following areas:

- 2096  
2097
- 2098 • interventions for conditions resulting from pregnancy;
  - 2099 • interventions for conditions that affect the general population and can be reasonably expected  
2100 to be used without adequate supporting evidence during pregnancy (for example off-label use  
2101 of medications);
  - 2102 • interventions for conditions that affect the developing fetus;
- 2103

2104 *Informed consent and risks and potential benefits.* The involvement of pregnant women in research is  
2105 complicated by the fact that it may present risks and potential benefits to the fetus as well as to the  
2106 woman and to the future person the fetus may become. Participation of lactating women in biomedical  
2107 research may equally pose risks to the nursing infant. Research in pregnant and lactating women must  
2108 be initiated after careful consideration of the best available data from: preclinical research in pregnant  
2109 animal models, research in non-pregnant women, retrospective observational studies, and adverse  
2110 events registries.

2111 Researchers and research ethics committees must ensure that potential research participants are  
2112 adequately informed about the risks to lactating women and their infants and about the risks to  
2113 pregnant women (including future fertility), their pregnancies, their fetuses, and their future offspring.  
2114 Disclosure must also include information about what has been done to maximize potential benefits and  
2115 minimize risks (see guideline 4). Even when evidence concerning risks is unknown or controversial, this  
2116 must be disclosed to the pregnant or lactating woman as part of the informed consent process. She will  
2117 make the final decision about the acceptability of these risks for her and her fetus or infant. Women  
2118 must also be informed that it is often difficult to determine causality in cases of fetal or infant  
2119 abnormalities. Pregnant women may be recruited for research in which there is no prospect of  
2120 individual benefit to them or the fetus only if the risks of the intervention are minimal. Examples include  
2121 minimally invasive studies of new diagnostic techniques. In special circumstances, a minor increase  
2122 above minimal risk may be acceptable.

2123 Some research involving pregnant women may be directed at the health of the fetus. In such cases, the  
2124 role of the woman remains the same: she is the decision maker for any interventions that affect her.  
2125 This does not exclude the possibility of the woman consulting with the father of the fetus, if she wishes.

2126

2127 Especially in communities or societies in which cultural beliefs accord more importance to the fetus  
2128 than to the woman's life or health, women may feel constrained to participate, or not to participate, in  
2129 research. Special safeguards must be established to prevent undue inducement to pregnant women to  
2130 participate in research in which interventions hold out the prospect of direct benefit to the fetus and not  
2131 to the woman herself.

2132 Researchers must include in protocols on research involving pregnant women a plan for monitoring the  
2133 outcome of the pregnancy with regard to both the health of the woman and the short-term and long-  
2134 term health of the infant and child.

2135 *Minimal risk and a minor increase above minimal risk.* Research risks are minimal when the risk of  
2136 serious harm is very unlikely and the potential harms associated with more common adverse events  
2137 are low (see guideline 4). Risks in research must be compared to risks that an average, normal, healthy  
2138 pregnant or lactating woman experiences in daily life or during routine examinations. If the risks are  
2139 considered as minimal in these situations, they may also be considered as minimal in research  
2140 involving pregnant or lactating women. A research ethics committee may permit a minor increase  
2141 above minimal risk for research procedures that have no prospect of benefit when the necessary data  
2142 cannot be gathered in non-pregnant or non-lactating women, and the social value of the research for  
2143 pregnant or lactating women is compelling. While there is no precise definition of a "minor increase"  
2144 above minimal risk, the increment in risk must only be a fraction above the minimal risk threshold and  
2145 considered acceptable by a reasonable person (see guideline 4).

2146 *Serious harm and access to abortion.* Research with pregnant women must be conducted only in  
2147 settings where these women can be guaranteed access to a safe, legal abortion. This rule serves to  
2148 prevent women from having to carry to term and deliver babies with known anomalies against their  
2149 wishes. Before pregnant women are enrolled, researchers must determine whether significant fetal  
2150 abnormality is recognized as an indication for abortion in that jurisdiction. If it is not, then, pregnant  
2151 women must not be recruited for research in which there is a realistic basis for concern that significant  
2152 fetal abnormality may occur as a consequence of participation in research. At the same time, this rule  
2153 might restrict potentially valuable research in countries where women cannot be guaranteed access to  
2154 abortion. In such cases research projects can be conducted only if a local research ethics committee  
2155 determines that the research has compelling social value for pregnant or women and the women are  
2156 informed about existing restrictions on abortion and possible options for obtaining an abortion in  
2157 another country.

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## 2161 **Guideline 20: Research in disaster situations**

2162 **Disasters such as epidemics, earthquakes, tsunamis, and military conflicts can have a sudden**  
2163 **and devastating impact on the health of large populations. In order to identify effective ways of**

2164 **mitigating the health impact of disasters, health-related research must form an integral part of**  
2165 **disaster response.**

2166 **While conducting research in disasters, it is essential to uphold the ethical principles embodied**  
2167 **in these guidelines. The importance of generating knowledge quickly and maintaining public**  
2168 **trust, as well as the practical challenges of conducting research in a situation of crisis, need to**  
2169 **be carefully balanced with ensuring the scientific validity and ethical conduct of studies. The**  
2170 **conduct of research must not unduly compromise the response to the victims of a disaster.**

2171 **In particular, researchers, sponsors, and research ethics committees must ensure that:**

- 2172 • **studies are designed so as to yield scientifically valid results under the challenging and**  
2173 **often rapidly evolving conditions of a disaster (see guideline 1)**
- 2174 • **the research is responsive to the health needs or priorities of the disaster victims and**  
2175 **cannot be conducted outside a disaster situation (see guideline 2)**
- 2176 • **participants are selected fairly and adequate justification is given if particular**  
2177 **populations (for example health workers) are targeted (see guideline 3)**
- 2178 • **burdens and benefits in the selection of groups of subjects as well as the possible**  
2179 **benefits of the research are equitably distributed (see guideline 3)**
- 2180 • **the risks and potential benefits of experimental interventions are assessed realistically,**  
2181 **especially when they are in the early phases of development (see guideline 4)**
- 2182 • **communities are actively engaged in study planning, while recognizing the associated**  
2183 **practical challenges and ensuring cultural sensitivity (see guideline 7)**
- 2184 • **the individual informed consent of participants is obtained even in a situation of duress**  
2185 **(see guideline 9)**  
2186

2187 **Research in disasters must ideally be planned ahead. Health officials and research ethics**  
2188 **committees must develop procedures to ensure appropriate, timely and flexible mechanisms**  
2189 **and procedures for ethical review and oversight. For example, research ethics committees**  
2190 **could pre-screen study protocols in order to facilitate and expedite ethical review in a situation**  
2191 **of crisis. Similarly, researchers and sponsors could make pre-arrangements on data and sample**  
2192 **sharing that research ethics committees review in advance.**

2193 *Commentary on guideline 20*

2194 *Humanitarian response and research.* Disasters are sudden events that cause great suffering or loss of  
2195 life. Disease and illness can either be the cause of disasters, or they can be a result from disasters of  
2196 other origin. For example, epidemics can lead to disasters and destabilize political institutions or  
2197 undermine economic activity. Conversely, natural and man-made disasters, such as earthquakes and  
2198 war, can weaken or destroy health systems and have a devastating impact on individual and population  
2199 health. The first and foremost obligation in disaster situations is to respond to the needs of those  
2200 affected. At the same time, there is an obligation to conduct health-related research because disasters  
2201 can be difficult to prevent and the evidence base for effectively preventing or mitigating their public  
2202 health impact is limited. These two obligations can come into conflict. In particular, humanitarian  
2203 response and health-related research often rely on the same infrastructure and the same personnel, so  
2204 that priorities between the two may need to be set. If nurses and physicians become researchers this  
2205 may also create dependent relationships (see guideline 9). Humanitarian workers, researchers and  
2206 sponsors must be aware of these conflicts and ensure that their studies do not unduly compromise the  
2207 disaster response. Researchers and sponsors should also aim to add to the infrastructure for the  
2208 humanitarian response. Moreover, all studies must be responsive to the health needs or priorities of the  
2209 affected populations, and it must not be possible to conduct the research outside a disaster situation.

2210

2211 *General challenges in disaster research.* In infectious disease outbreaks, there can be a lot of pressure  
2212 to conduct research. This is especially the case when diseases have a high mortality rate and the  
2213 treatment options are limited (for example 2014 Ebola outbreak). Conversely, in natural or man-made  
2214 disasters, research can be met with great skepticism or even hostility. Researchers and sponsors must  
2215 be equipped to negotiate these pressures in what are typically fragile political and social situations.  
2216 Furthermore, disasters pose numerous challenges for conducting ethically responsible research. For  
2217 example, potential study participants often suffer from serious physical or psychological trauma that can  
2218 make it difficult for them to protect their rights and interests. Limited health infrastructure can require  
2219 making compromises in data collection and study design. Despite these and challenges, it is essential  
2220 that researchers and sponsors uphold the ethical principles embodied in these guidelines, even if the  
2221 standard ways of respecting these principles may need to be modified. In fact, the disaster situation can  
2222 require modifying standard procedures so that the ethical principles can be upheld in the most  
2223 expedient way possible. For example, while ethical oversight is essential in all research, accelerated  
2224 ethical review during disasters may be necessary to ensure that valuable ethical studies can begin as  
2225 soon as possible.

2226 While all ethical principles in this guideline have to be upheld, some require special attention.

2227 *Potential benefits and risks of investigational interventions and emergency use outside clinical trials.*  
2228 Especially when disasters are caused by an infectious disease that is highly contagious or serious (for  
2229 example influenza, Ebola), there is great pressure to develop effective treatments and vaccines.  
2230 Moreover, when facing a serious threat, many people are willing to assume high risks and use  
2231 unproven agents within or outside of clinical trials. However, it is essential that researchers and  
2232 sponsors realistically assess the potential benefits and risks of experimental interventions and  
2233 communicate these clearly to potential participants and individuals at risk. Even under ordinary  
2234 circumstances, many promising experimental agents do not prove to be safe and effective. Moreover,  
2235 experimental interventions must be systematically evaluated in clinical trials. Widespread emergency  
2236 use with no or limited data collection about patient outcomes must therefore be avoided.

2237 *Equitable distribution of risks and benefits.* Because experimental interventions are often limited in  
2238 disaster situations, fair selection of participants is essential (guideline 3 on equitable distribution).  
2239 Especially in dire emergencies, well-off and well-connected patients must not be further privileged and  
2240 the exclusion of vulnerable populations must be justified (guideline 15 on vulnerable persons). It may  
2241 be acceptable to prioritize certain populations in study enrolment. For example, health professionals  
2242 often put themselves at risk during a disaster (for example epidemic), and they could help more  
2243 patients once recovered. The principles of reciprocity and helping the largest number of people could  
2244 therefore justify their prioritization. At the same time, health workers are often well-off and have special  
2245 ties to the medical establishment. Their priority might therefore further privilege the well-off, especially  
2246 when compared to those who put themselves at risk without being trained as health professionals (for  
2247 example burial teams during an epidemic). Researchers, sponsors, and Research ethics committees  
2248 need to ensure that burdens and benefits in the selection of groups of subjects are equitably distributed  
2249 (see guideline 1).

2250 *Scientific validity.* Disasters unfold quickly and study designs need to be chosen so that studies will  
2251 yield meaningful data in a rapidly evolving situation. Moreover, study designs must be feasible in a  
2252 disaster situation but still appropriate to ensure the study's scientific validity. Without scientific validity,  
2253 the research lacks social value and must therefore not be conducted (see guideline 1 on social value).  
2254 The research may even detract personnel or resources from the disaster response. In clinical trials, the  
2255 randomised-controlled trial design remains the "gold standard" for collecting robust data. However,  
2256 researchers, sponsors, Research ethics committees and others must explore alternative trial designs  
2257 that may increase trial efficiency and access to promising experimental interventions while sufficiently  
2258 maintaining scientific validity. The methodological and ethical merits of alternative trial designs must be  
2259 carefully assessed before these designs are used. For example, when testing experimental treatments

2260 or vaccines during an epidemic, the appropriate trial design will depend on the promise of the  
2261 investigational agent, the variation of critical background variables (for example mortality and infection  
2262 rates), and measurement and other practical challenges, among other factors. Researchers and  
2263 sponsors must carefully evaluate the relative merits of different designs (for example observational or  
2264 placebo-controlled) based on these factors.

2265 *Community engagement.* Because disasters often lead to vulnerability and fragile political and social  
2266 situations, engaging local communities about the research is essential for maintaining public trust and  
2267 ensuring that studies are conducted in a culturally sensitive manner (see guideline 7 on community  
2268 engagement). Researchers and sponsors can use creative mechanisms and processes to expedite and  
2269 facilitate community engagement in a disaster situation (for example social media). Fostering  
2270 community leadership will often be important to address distrust and effectively discuss complex and  
2271 controversial issues, for example in order to gain support for the study design.

2272 *Ethical review and oversight.* The standard mechanism for ethical review will often be too time  
2273 consuming to enable research during disasters, and procedures to ensure appropriate, timely and  
2274 flexible study protocols in order to facilitate and accelerated ethical review in a situation of crisis.  
2275 However, pre-screening cannot substitute for ethical review with specific information added at the time  
2276 of the ethical review oversight are therefore needed. For example, research ethics committees or a  
2277 specialist ethics committee (perhaps on a national or regional level) may conduct an initial accelerated  
2278 review of study protocols and continue oversight if studies raise significant ethical concerns. Research  
2279 in disaster situations must be planned in advance. This can involve, among other things, submitting  
2280 study protocols or protocol parts for ethical pre-screening and drafting arrangements for data and  
2281 sample sharing between collaborators. Research ethics committees might thus pre-screen disaster.  
2282 Health officials might also create an international network of specialists that could inform local review  
2283 during a disaster.

2284 *Informed consent.* Even though most disaster victims are under duress, it is important to obtain their  
2285 informed consent for study participation and, in particular, emphasize the difference between research  
2286 and humanitarian intervention. This is especially important in the context of clinical trials that test  
2287 experimental interventions in the early phases of development. The fact that potential participants are  
2288 under duress does not preclude them from making a voluntary decision (guideline 9 on informed  
2289 consent). The informed consent process must be designed in a way that is comprehensible and  
2290 sensitive to persons who are under duress. When information leaflets are too long, a summary must be  
2291 provided (see guideline 9). Incompetent participants, for example orphans without a surrogate decision  
2292 maker, are entitled to protection. Special protections for incompetent participants may apply, as  
2293 described in guideline 16 in the section on *Emergency care situations in which the researcher*  
2294 *anticipates that many participants will be unable to consent*

2295

2296 (See also guideline 17: Research involving children).

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## 2299 **Guideline 21: Implementation research**

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2301 **Implementation research investigates an intervention previously shown to be effective in a**  
2302 **different research setting to determine whether it can be successfully adapted to a new setting.**  
2303 **The same ethical principles that govern all research are applicable to implementation research.**  
2304 **However, special problems arise when a cluster randomised design is employed. In this**

2305 **research design, groups of individuals (clusters) or communities are randomised to different**  
2306 **interventions.**

2307 **In advance of initiating an implementation trial, researchers, sponsors, relevant authorities, and**  
2308 **research ethics committees must**

- 2309 • **determine who are the research subjects and whether informed consent must be**  
2310 **obtained from patients, health care workers, or members of both groups in certain**  
2311 **studies**
- 2312 • **determine whether requiring informed consent and allowing refusal to consent may**  
2313 **invalidate or compromise the research results**
- 2314 • **determine whether a no-intervention group is ethically acceptable as a comparator in**  
2315 **implementation research**
- 2316 • **decide whether permission must be obtained from a gatekeeper**
- 2317 • **consider the possibilities to de-implement the intervention if it turns out to be inferior**  
2318 **than care as usual**  
2319

2320 *Commentary on guideline 21*

2321 *Implementation research.* Many implementation research studies involve the training of healthcare  
2322 workers in diagnostic or therapeutic methods of proven efficacy elsewhere. The aim of such research is  
2323 not to demonstrate efficacy but rather, to ascertain whether the healthcare workers have learned to use  
2324 the technique properly. The line between implementation research and quality improvement in a health  
2325 facility is often blurred. The head of a hospital or unit may decide to train physicians or nurses in order  
2326 to introduce an intervention that has been proven elsewhere. In that type of quality improvement, there  
2327 is typically no randomization, usually no review by a research ethics committee, and no informed  
2328 consent obtained from the health care workers, who are the targets of the intervention. However, when  
2329 different floors of the hospital or different health care facilities are randomised, with some getting the  
2330 new training and others doing their routine procedures, the act of randomization transforms quality  
2331 improvement into implementation research. It would then require review by a research ethics  
2332 committee, which would have to determine whether consent is needed from patients and whether  
2333 consent from health care workers may be waived.

2334 *Identifying the research participants.* As in all research involving human participants, individuals who  
2335 are targeted by an intervention are considered to be human subjects of research. In cluster randomised  
2336 trials, the subjects can be patients, health care workers, or both. When an implementation study is  
2337 conducted at a cluster level (different hospitals, clinics, or communities) it can be difficult if not  
2338 impossible to obtain consent from health care workers. If some health care workers refuse to be  
2339 observed or to apply a new diagnostic or therapeutic tool, that could confound the results of the  
2340 research. Researchers would not be able to tell whether the intervention is sufficiently effective if some  
2341 health care workers employ their usual procedures. A waiver of consent would then be an option (see  
2342 guideline 4), but health care workers must nevertheless be notified that a study is taking place. If the  
2343 interventions are directly carried out on patients, they would normally also be considered research  
2344 subjects.

2345 Patients may not be directly intervened upon in some implementation research but aggregate data from  
2346 patients' records may be used to judge the effectiveness of the intervention. An example is the  
2347 introduction of new infection control procedures for workers in one cluster, with no change in  
2348 procedures for the control cluster. Because only aggregate data is recorded regarding the number of  
2349 infections, no consent is required from the patients.

2350 *Informed consent.* As a general rule, researchers must obtain informed consent from human research  
2351 participants in implementation research using a cluster-randomised design, unless a waiver or

2352 modification of consent is granted by a research ethics committee (see guideline 10). Waivers or  
2353 modifications of informed consent may be common in cluster randomised trials because researchers  
2354 may want to avoid participants in the control group learning about the intervention in the intervention  
2355 group and accordingly change their behavior or try to get the intervention at another location. Another  
2356 reason for the use of waivers or modifications of consent in cluster randomised trials is that it is  
2357 sometimes virtually impossible to obtain individual informed consent. This occurs when the intervention  
2358 is directed at an entire community, making it impossible to avoid the intervention. Examples include a  
2359 study comparing methods of incinerating waste or fluoridating the drinking-water supply to prevent  
2360 dental carries. Members of the intervention community cannot avoid being affected by the intervention,  
2361 so obtaining individual informed consent is impossible. Similarly, if the units in a cluster are hospitals or  
2362 health centers, it could be difficult for patients to find another hospital or general practice to avoid a new  
2363 method of delivery of preventive services.

2364 Although in most cluster randomised trials participants cannot consent to being randomised, depending  
2365 on the type of study design they may be able to give informed consent to receive the intervention. The  
2366 intervention may be delivered at the individual level while the communities to which the individuals  
2367 belong are randomised at the cluster level (for example a vaccination campaign applied at the school  
2368 level). These trials are called *individual-cluster randomised trials*. In some *individual-cluster randomised*  
2369 *trials*, individuals may be able to consent to the intervention before it is administered in that cluster. For  
2370 example, parents will not be able to consent to their children's school being randomised to a  
2371 vaccination program or to being allocated to that cluster, but they could consent or refuse to consent to  
2372 their child's vaccination at school. In cluster randomised trials it may also be the case that both the  
2373 intervention and the community are randomised at the cluster level. These trials are called *cluster-*  
2374 *cluster randomised trials* (for example all the students in a school or all residents of a community). In  
2375 *cluster-cluster randomised trials* individual informed consent for receiving the intervention is typically  
2376 difficult to obtain since it is almost impossible to avoid the intervention. At the same time, it is important  
2377 to see that individual consent for data collection procedures is usually possible in both types of cluster  
2378 randomised trials.

2379 *Ethical acceptability of a no-intervention group.* By definition, implementation research investigates  
2380 interventions that have been proven to be effective elsewhere. A question therefore arises whether it is  
2381 ethically acceptable to withhold the proven intervention from a control group in a cluster randomised trial.  
2382 This situation is analogous to that of placebo controls in a randomised, controlled trial when an  
2383 established, effective prevention or treatment exists. If withholding the proven intervention from the  
2384 control cluster would expose participants to more than a minor increase above minimal risk, it would be  
2385 unethical to use that study design. An example would be the introduction of sterilizing equipment or  
2386 disposable needles in a resource poor health center with a high infection rate among the patients. In  
2387 the implementation study, health care workers would have to be educated in the use of the new  
2388 equipment and instructed to throw away the disposable needles. Since the reuse of needles without  
2389 sterilization would expose patients to more than a minor increase above minimal risk, it would be  
2390 unethical for the control cluster to continue the usual practice. In such cases, it is necessary for  
2391 researchers to explore an alternative design, such as using historical controls from the same facility.  
2392 Research ethics committees have the responsibility to determine whether the proposed research is  
2393 ethically acceptable when the methodology calls for withholding the established effective treatment  
2394 from the control cluster.

2395 *Gatekeeping in cluster randomised trials.* When a cluster randomised trials substantially affects cluster  
2396 or organizational interests, and a gatekeeper (for example a community leader, headmaster, or local  
2397 health council) possesses the legitimate authority to make decisions on the cluster or organization's  
2398 behalf, the researcher must obtain the gatekeeper's permission to enroll the cluster or organization in  
2399 the trial. Such permission does not replace the need to obtain individual informed consent where this is  
2400 required. While this gatekeeper may not have been appointed or elected for the specific purpose of  
2401 giving permission for the cluster to participate in research, the scope of authority must encompass



2402 interventions of the type in question if provided outside of a research project; moreover, the decision-  
2403 maker must ensure that the risks of participation in the study and the randomization are commensurate  
2404 with the benefits for the cluster or for society. The gatekeeper may choose to consult a wider group of  
2405 community representatives or advisers before taking the decision to permit the study.

2406

## 2407 **Guideline 22: Use of online information or tools in health-related research**

2408 **The ethical principles embodied in these guidelines are applicable to health-related research**  
2409 **using online information or tools. However, such research can have unique features that require**  
2410 **special consideration.**

2411 *Commentary on guideline 22*

2412 *General considerations.* Information available on, or collected through, online platforms offers  
2413 opportunities and challenges for health-related research. Some information is provided directly by  
2414 users. For example, users of health apps, online patient groups, or health-related information sites  
2415 supply health-related data to these sites or apps. Other information is generated by tracking online  
2416 behavior, such as the purchase of prescription drugs through online pharmacies. Researchers may  
2417 observe what online users are saying or doing without interacting directly with them. Conversely,  
2418 researchers may use online tools or platforms as a way of conducting studies, such as online surveys.

2419 *Scientific validity of the research using online information or tools.* One potential problem with health-  
2420 related research using online information or tools is that the veracity of the data can be more difficult to  
2421 confirm than in research involving face-to-face interaction. For example, respondents to an online  
2422 survey may not satisfy the inclusion or exclusion criteria for the given research project. Minors might  
2423 respond to studies intended to recruit adults. People can – consciously or unconsciously - pretend to be  
2424 what they are not. Such responses can compromise or undermine the accuracy of online data.  
2425 Therefore, researchers must discuss the validity of their data in their report.

2426 *Consent and ethical review.* The context in which information is provided or obtained is important, and  
2427 whether or not the consent to the use or collection of online information is acceptable depends on  
2428 reasonable expectations for how this information is used in the given context. There is a relevant  
2429 difference between situations in which researchers i) analyze information that is clearly publicly  
2430 accessible and perceived as such, ii) analyze information that users have provided in a semi-private  
2431 space, and iii) collect information specifically for research purposes.

2432 i) Information publicly available on the internet and known to be publicly accessible by the users,  
2433 meaning that researchers only observe and do not interact with human subjects. In such cases,  
2434 researchers can use the information after accelerated ethical review and without individual informed  
2435 consent (see guideline 4). Exemptions from ethical review may be applicable (see guideline 23).

2436 ii) On other online platforms, a certain inner, seemingly private circle is created online, in which users  
2437 reasonably expect only limited access to information. Examples are social media sites where users  
2438 create an online circle of friends by invitation or users pay to join an online community that is dedicated  
2439 to the exchange of health-related information. On these platforms, service providers must offer  
2440 authorization mechanism such that users must be explicitly informed about the possibility that research  
2441 may be done with their information and ideally similar to broad informed consent to research with  
2442 biological material (see guideline 11). Users must give specific permission for such research. This  
2443 explicit broad informed consent procedure must be separate from agreeing to the terms of use.

2444 When providers of online platforms or services make user information accessible for research, it is  
2445 recommended that they establish appropriate governance structures to evaluate and monitor studies on

2446 their users' information. For example, a qualified member of staff could be charged with evaluating  
2447 study protocols before granting researchers access and, where necessary, refer protocols for standard  
2448 research ethics review. Researchers must make their presence explicit while conducting studies on  
2449 semi-private online platforms or services, for example by posting an announcement in a "news for  
2450 users" section. Researchers must not actively recruit participants for other research on these kinds of  
2451 platforms unless this possibility is clearly indicated in the broad informed consent.

2452 iii) When researchers use online tools to collect data specifically for research purposes, such as online  
2453 surveys, these studies must undergo ethical review, consistent with national legislation or regulations,  
2454 just like other research. In order to protect confidentiality, survey participants could be advised to adopt  
2455 a fictional name. When researchers use online tools to actively recruit participants for their research, a  
2456 user must receive information on research participation with specific options relevant to his or her  
2457 situation and informed consent must be sought. Exemptions from review may be applicable (see  
2458 guideline 23).

2459 *Data management.* Participants' privacy, confidentiality and other interests can be at stake when data  
2460 are conveyed to others electronically. Researchers must make sure that confidentiality of information is  
2461 guaranteed during data collection, storage and sharing (see guideline 24 on public accountability) and  
2462 the combination of databases. Registration forms and questionnaires with personal identifiers must  
2463 receive a high degree of security. Researchers and sponsors must use secure passwords and the best  
2464 available encryption technology in order to ensure that only authorized persons are able to access the  
2465 data (see guideline 12).

2466 *Public accountability.* After completion of a study, the accuracy and completeness of the information  
2467 made available on the Internet become relevant. Researchers must be explicit in indicating whether the  
2468 information provided is preliminary or final and indicate the date of uploading the data (see also  
2469 guideline 24).

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2475 **Guideline 23: Requirements for establishing research ethics committees and their review of**  
2476 **protocols**

2477 **All proposals to conduct health-related research involving humans must be submitted to a**  
2478 **research ethics committee to review their ethical acceptability, unless there are exemptions as**  
2479 **specified by applicable law or regulations. The researcher must obtain approval or clearance by**  
2480 **such a committee before beginning the research. The research ethics committee must conduct**  
2481 **further reviews as necessary, in particular if there are significant changes in the protocol.**

2482

2483 **Research ethics committees must review research protocols according to the principles set out**  
2484 **in these guidelines.**

2485

2486 **Research ethics committees must be formally established and given adequate mandate and**  
2487 **support to ensure timely and competent review according to clear and transparent procedures.**  
2488 **Committees must include multidisciplinary membership in order to competently review the**

2489 **proposed research. Committee members must be duly qualified and regularly update their**  
2490 **knowledge of ethical aspects of health-related research. Research ethics committees must have**  
2491 **mechanisms to ensure independence of their operations.**

2492

2493 **Research ethics committees from different institutions or countries must establish efficient**  
2494 **communication in cases of externally sponsored and multi-center research. In externally**  
2495 **sponsored research, appropriate ethical review take place in both the host and the sponsoring**  
2496 **community.**

2497

2498 **Research ethics committees must have a clear procedure for researchers or sponsors to make**  
2499 **legitimate appeals to the decisions of research ethics committees.**

2500

2501 *Commentary on Guideline 23*

2502 *General considerations.* Research ethics committees may function at the institutional, local, regional, or  
2503 national level, and in some cases at the international level. They must be established in accordance  
2504 with rules set by a national or other recognized authority. Regulatory or other governmental authorities  
2505 must promote uniform standards for committees within a country. Research institutions and states must  
2506 allocate sufficient resources for the ethical review process. Contributions of study sponsors to  
2507 institutions or governments in order to support ethics review must be made in a transparent process.  
2508 Under no circumstances may payment be offered or accepted to procure a committee's approval or  
2509 clearance of a protocol.

2510 *Scientific and ethical review.* Although in some instances scientific review precedes ethical review,  
2511 research ethics committees must always have the opportunity to combine scientific and ethical review  
2512 in order to ensure the social value of the research (guideline 1). The ethical review must consider,  
2513 among other aspects, the study design, provisions for minimizing risk and that any remaining risks are  
2514 appropriately balanced in relation to the potential benefits for participants and the social value of the  
2515 research, issues of safety (safety of the study site and medical interventions and monitoring safety  
2516 during the study), and the feasibility of the research. Scientifically unsound research involving human  
2517 subjects is unethical in that it may expose them to risk or inconvenience for no purpose. Even if there is  
2518 no risk of injury, involving subjects' and researchers' time in unproductive activities wastes valuable  
2519 resources. Research ethics committees must therefore recognize that the scientific validity of the  
2520 proposed research is essential for its ethical acceptability. Committees must either carry out a proper  
2521 scientific review, verify that a competent expert body has determined the research to be scientifically  
2522 sound, or consult with competent experts to ensure that the research methods are appropriate. If  
2523 research ethics committees do not have expertise to judge science or feasibility, they must draw on  
2524 relevant expertise.

2525 *Accelerated review.* Accelerated review is a process by which studies that involve no more than  
2526 minimal risk may be reviewed and approved in a timely manner by an individual research ethics  
2527 committee member or a designated subset of the full committee. Relevant authorities or research ethics  
2528 committees may establish procedures for the accelerated review of research proposals. These  
2529 procedures should specify the following:

- 2530 - the nature of the applications, amendments, and other considerations that will be eligible for  
2531 accelerated review;
- 2532 - the minimum number of research ethics committee members for accelerated review;
- 2533 - the status of decisions (for example, subject to confirmation by a full research ethics committee  
2534 or not).

2535 Relevant authorities or research ethics committees must establish a list of criteria for protocols that  
2536 qualify for an accelerated review process.

2537 *Further review.* The research ethics committee must conduct further reviews of approved studies as  
2538 necessary, in particular if there are significant changes in the protocol that could impact the validity of  
2539 the consent, the safety of participants, or other ethical matters that emerge during the course of the  
2540 study. These further reviews include progress reports and possible monitoring of researchers'  
2541 compliance with approved protocols.

2542 *Committee membership.* The research ethics committee must be constituted according to a document  
2543 that specifies the manner in which members and the chair will be appointed, reappointed, and replaced.  
2544 Research ethics committees must have members capable of providing competent and thorough review  
2545 of research proposals submitted to them. Membership normally must include physicians, scientists and  
2546 other professionals such as research coordinators, nurses, lawyers, and ethicists, as well as (lay)  
2547 persons who can represent the cultural and moral values of the community. Committees must include  
2548 both men and women. When a proposed study involves vulnerable individuals or groups, as may be the  
2549 case in research involving prisoners or illiterate persons, representatives from appropriate advocacy  
2550 groups must be invited to meetings where such protocols will be reviewed (see guideline 15). Regular  
2551 rotation of members is desirable for balancing the advantage of experience with that of fresh  
2552 perspectives.

2553 Members of research ethics committees must regularly update their knowledge about the ethical  
2554 conduct of health-related research. If committees do not have the relevant expertise to adequately  
2555 review a protocol, they must consult with external persons with the proper skills or certification.  
2556 Research ethics committees must keep records of their deliberations and decisions.

2557 *Conflicts of interests from research ethics committee members.* Research ethics committees must have  
2558 mechanisms to ensure the independence of their operations. In particular they must avoid any undue  
2559 influence and minimize and manage conflicts of interests. Research ethics committees must require  
2560 that their members disclose to the committee any interests they may have that could constitute a  
2561 conflict of interest or otherwise bias their evaluation of a research proposal. Research ethics  
2562 committees must evaluate each study in light of any disclosed interests and ensure that appropriate  
2563 steps are taken to mitigate possible conflicts of interest (see guideline 25 on conflicts of interest).  
2564 Research ethics committees may receive a fee for reviewing studies. This does not necessarily create  
2565 a conflict of interest (see guideline 25).

2566 *National (centralized) or local review.* Research ethics committees may be created under the aegis of  
2567 national or local health administrations, national (or centralized) medical research councils or other  
2568 nationally representative bodies. In a highly centralized administration a national, or centralized, review  
2569 committee may be constituted for both the scientific and the ethical review of research protocols. In  
2570 countries where medical research is not centrally administered, ethical review can also be undertaken  
2571 at a local or regional level. Whether research is nationally or locally reviewed varies per country and  
2572 may depend on the size of the country and the type of the research. The authority of a local research  
2573 ethics committee may be confined to a single institution or may extend to all institutions in which  
2574 biomedical research is carried out within a defined geographical area or network.

2575

2576 *Externally sponsored research.* Research may be externally sponsored, meaning that that it is  
2577 sponsored, financed, and sometimes wholly or partly carried out by an external organization with the  
2578 collaboration or agreement of the appropriate authorities of the host community. External sponsors  
2579 must collaborate with local partners (see guideline 8).

2580 Externally sponsored research must be reviewed at the site of the sponsor as well as locally. Local  
2581 committees must be fully empowered to disapprove a study that they believe to be unethical.

2582 *Multi-centre research* Some research projects are designed to be conducted in a number of centres in  
2583 different communities or countries. To ensure that the results will be valid, the study must be conducted  
2584 in a methodologically identical way at each centre. However, committees at individual centres must be  
2585 authorized to make changes to a template of the informed consent document provided by the sponsor  
2586 of the lead institution in the multi-centre trial.

2587 To avoid lengthy procedures, multi-centre research in a single jurisdiction should be reviewed by one  
2588 research ethics committee only. In cases of multi-centre research, if a local review committee makes  
2589 changes to the original protocol that they believe are necessary to protect the research participants,  
2590 these changes must also be reported to the research institution or sponsor responsible for the whole  
2591 research program for consideration and due action. This is to ensure that all other subjects can be  
2592 protected and that the research will be valid across sites.

2593 Ideally review procedures are harmonized, which may decrease the time needed for review and  
2594 accordingly speed up the research process. In order to harmonize review processes and to maintain  
2595 sufficient quality of these processes, ethics committees must develop quality indicators for ethical  
2596 review. Appropriate review has to be sensitive to increases in risk of harm or wrong to local participants  
2597 and populations. To ensure the validity of multi-centre research, explicit inter-centre comparability  
2598 procedures must be introduced for changes made in the protocol.

2599 *Exemptions from review.* Internet research (see guideline 22) or some epidemiological studies may be  
2600 exempt from ethical review if publicly available data is analyzed or the data for the study are generated  
2601 by observation of public behavior, provided that in doing so or in reporting results, data about individual  
2602 persons or groups of persons is anonymized or coded. Health systems research studies may be  
2603 exempted from review if public officials are interviewed in their official capacity on issues that are in the  
2604 public domain.

2605 *Protocol amendments, deviations, violations and sanctions.* During the study deviations from the  
2606 original study might occur, such as changes in the sample size or analysis of the data as described in  
2607 the protocol. Deviations must be reported to research ethics committees. In the case of permanent  
2608 deviations researchers may write an amendment. The research ethics committee must then decide  
2609 whether a deviation is legitimate or illegitimate. Deviations are therefore not always protocol violations.  
2610 Protocol violations are deviations from the original protocol that significantly affect the rights or interests  
2611 of research participants and/or significantly impact the scientific validity of the data.

2612

2613

2614 Apart from protocol violations, a researcher may also fail to submit a protocol to a research ethics  
2615 committee. This omission must be considered a clear and serious violation of ethical standards, unless  
2616 applicable regulations specify conditions for exemptions from review.

2617

2618 Research ethics committees generally have no authority to impose sanctions on researchers for  
2619 protocol violations or violations of ethical standards in the conduct of research involving humans.  
2620 However, committees may halt the continuation of a previously approved protocol if it finds protocol  
2621 violations or other misconduct on the part of researchers. Committees must report to institutional or  
2622 governmental authorities any serious or continuing non-compliance with ethical standards in the  
2623 conduct of previously approved research projects.

2624

2625 **Guideline 24: Public accountability for health-related research**

2626 **In order to promote societal trust in health-related research, researchers, sponsors, research**  
2627 **ethics committees, editors and publishers have an obligation to ensure public accountability for**  
2628 **research and its results. In particular, researchers must prospectively register their studies,**  
2629 **publish the results and share the data on which these results are based in a timely manner.**  
2630 **Negative and inconclusive as well as positive results of all studies must be published or**  
2631 **otherwise be made publicly available.**

2632

2633 *Commentary on guideline 24*

2634 *General considerations.* It is in the interest of all to improve the effectiveness of health care and public  
2635 health to attain their fundamental goals: to prevent and cure disease where possible and otherwise  
2636 alleviate pain and suffering (see guideline 1). Health-related research plays a vital role in this and  
2637 therefore it is in the interest of society to promote such research for the benefit of all. At the same time,  
2638 health-related research comes with risks and burdens for participants and with professional or financial  
2639 benefits for the researchers and sponsors. Health-related research only functions in the presence of  
2640 professional and public trust. Trust can be enhanced by ensuring public accountability for research and  
2641 its results. Therefore, researchers, sponsors, research ethics committees, editors and publishers all  
2642 have ethical obligations with regard to the public accountability of research. This materializes in the  
2643 obligations to prospectively register studies, publish their results, and share the data on which these  
2644 results are based.

2645 *Trial registries.* An estimated half of clinical trials are never published, and those with negative or  
2646 unpromising results are more likely to disappear (a phenomenon called 'publication bias.')

2647 These unpublished data may contain important information on harms or side effects, clues about failed studies  
2648 or unpromising interventions that must not be re-tested, and information that other researchers could  
2649 use to increase the quality of research findings. As a first measure towards public accountability,  
2650 researchers and sponsors therefore have an obligation to register their studies before they actually  
2651 start, thus enabling others to see what is going on and make inquiries if reports fail to come out of the  
2652 study.

2653 Prospective registration of clinical trials enables comparison of data reported with hypotheses the  
2654 protocol was initially designed to test and help to establish the number of times a hypothesis has been  
2655 tested so that trial results can be understood in a broader context.

2656 *Publication and dissemination of the results of research.* A next step in achieving accountability is  
2657 publication and dissemination of the results of studies. Researchers have a duty to make the results of  
2658 their health-related research publicly available and are accountable for the completeness and accuracy  
2659 of their reports. Negative and inconclusive as well as positive results must be published or otherwise  
2660 made publicly available. In journal publications, all involved parties must adhere to the accepted  
2661 guidelines (such as ICMJE) for ethical reporting. Sources of funding, institutional affiliations and  
2662 conflicts of interest must be disclosed in the publication. Reports of research not in accordance with the  
2663 recognized guidelines must not be accepted for publication. Sponsors must not prevent researchers  
2664 from publishing unwelcome findings that restrict their freedom of publication. As the persons directly  
2665 responsible for their work, researchers must not enter into agreements that interfere unduly with their  
2666 access to the data or their ability to analyze the data independently, prepare manuscripts, or publish  
2667 them. Researchers must also communicate the results of their work to a lay audience. Researchers  
2668 should ideally promote and enhance public discussion.

2669 *Data sharing* There are compelling reasons to share the data of health-related research. Responsible  
2670 sharing of clinical trial data serves the public interest by strengthening the science that is the foundation

2671 of safe and effective clinical care and public health practice. Sharing also fosters sound regulatory  
2672 decisions, generates new research hypotheses, and increases the scientific knowledge gained from the  
2673 contributions of clinical trial participants, the efforts of clinical trial researchers, and the resources of  
2674 clinical trial funders. Data sharing involves more than sharing a summary of trial results, which is  
2675 already expected in publications (see above).

2676 Data sharing requires careful balancing of competing considerations. Sharing of study data presents  
2677 risks, burdens, and challenges as well potential benefits for various stakeholders. When sharing data,  
2678 researchers must respect the privacy and consent of study participants. Researchers want a fair  
2679 opportunity to publish their analyses and receive credit for carrying out studies and collecting data.  
2680 Other researchers want to analyze data that would otherwise not be published in a timely manner and  
2681 to replicate the findings of a published paper. Sponsors want to protect their intellectual property and  
2682 commercially confidential information and allow a quiet period to review marketing applications. All  
2683 stakeholders want to reduce the risk of invalid analyses of shared data.

2684 What is crucial is to create a culture of responsible data sharing and mutually reinforcing incentives for  
2685 sharing. Funders and sponsors must require funded researchers to share study data and provide  
2686 appropriate support for sharing. Researchers and sponsors must share data and design and carry out  
2687 future studies assuming that data will be shared. Research institutions and universities must encourage  
2688 researchers share data. Medical journals should require that authors share the analytic data set  
2689 supporting publications of study results. Patient advocacy organizations should consider data sharing  
2690 plans as a criterion for funding grants and promoting studies to their constituents. Regulatory agencies  
2691 around the globe should harmonize requirements and practices for data sharing. The risks of data  
2692 sharing may be mitigated through controls over with whom the data are shared and under what  
2693 conditions, without compromising the scientific usefulness of the shared data. Organizations that share  
2694 data should make use of data use agreements, observe additional privacy protections beyond de-  
2695 identification and data security as appropriate, and appoint an independent panel that includes  
2696 members of the public to review data requests. These safeguards must not unduly impede access to  
2697 data.

#### 2695 **Guideline 25: Conflicts of interest**

2696 **The primary goal of health-related research is to generate, in ethically appropriate ways, the**  
2697 **knowledge necessary to promote people’s health. However, researchers, research institutions,**  
2698 **sponsors, research ethics committees, and policy-makers can have secondary interests (for**  
2699 **example in scientific recognition or financial gain) that can conflict with the ethical conduct of**  
2700 **research. Such conflicts between the primary goal of health-related research and secondary**  
2701 **interests are defined as conflicts of interest.**

2702  
2703 **Conflicts of interest can influence the choice of research questions and methods, recruitment and**  
2704 **retention of participants, interpretation and publication of data, and the ethical review of research.**  
2705 **It is therefore necessary to develop and implement policies and procedures to identify, mitigate,**  
2706 **eliminate, or otherwise manage such conflicts of interest.**

2707  
2708 **Research institutions, researchers and research ethics committees must take the following steps:**

- 2709
- 2710 • **Research institutions must develop and implement policies and procedures to mitigate**
  - 2711 **conflicts of interest and educate their staff about such conflicts.**
  - 2712 • **Researchers must ensure that the materials submitted to a research ethics committee**
  - 2713 **include a disclosure of interests that may affect the research.**
  - 2714 • **Research ethics committees must evaluate each study in light of any disclosed interests**
  - 2715 **and ensure that appropriate means of mitigation are taken in case of a conflict of interest.**

- 2716
- **Research ethics committees must require their members to disclose their own interests to the research ethics committee and take appropriate means of mitigation in case of a conflict of interest (see guideline 23 on research ethics review)**
- 2717  
2718  
2719

2720 *Commentary on guideline 25*

2721 *General considerations.* A conflict of interest exists when there is a substantial risk that secondary  
2722 interests of one or more stakeholders in research unduly influence their judgment and thereby  
2723 compromise or undermine the primary goal of research. For example, a researcher may have a financial  
2724 stake in the outcomes of her study that creates a financial conflict of interest. Given the competitive  
2725 environment for academic researchers and the increasing commercialization of research, managing  
2726 conflicts of interests is essential for safeguarding the scientific integrity of research and protecting the  
2727 rights and interests of study participants. The commentary first explains conflicts of interests and then  
2728 discusses their management.

2729 *Conflicts of interest.* Different stakeholders in research can have different types of conflicts of interest.

2730

2731 1) *Researchers.* Academic conflicts of interest can arise when researchers – or senior members of  
2732 a research team – become too invested in their own ideas. For example, a researcher who has  
2733 worked for decades on an investigational HIV drug may find it difficult to stop a trial early when  
2734 interim results clearly recommend this course of action. Furthermore, researchers' careers  
2735 depend on publishing interesting results--for instance, when applying for research funding or  
2736 promotion. This can create professional conflicts of interests.

2737

2738 Some researchers also have personal financial conflicts of interest. For example, researchers  
2739 sometimes receive part of their salary or a "finder's fee" for recruiting research participants. When  
2740 this income reflects a fair compensation for their time spent on recruitment, it does not present an  
2741 inherent conflict of interest. However, a salary or "finders fee" may lead researchers –  
2742 intentionally or unintentionally – to interpret the inclusion or exclusion criteria of studies too  
2743 flexibly, thereby potentially exposing participants to excessive risks or compromising the scientific  
2744 validity of the research. This situation raises particular concern when participants are dependent  
2745 on the researcher who also is their clinician (see guideline 3 on dependent relationships), and  
2746 when the salary of the clinician is considerably lower as compared to that of the researcher. It  
2747 may also lead to researchers to exert pressure on eligible participants to enroll, thus  
2748 compromising or undermining participants' voluntary consent. In addition, financial conflicts of  
2749 interest can arise when researchers or senior members of the research team (or their close  
2750 family members) have a financial stake in the sponsor of the research, such as an equity interest.

2751

2752

2753 2) *Research institutions (for example universities, research centres, or pharmaceutical companies).*  
2754 Research institutions can have both reputational and financial conflicts of interests. For example,  
2755 universities rely on the reputation of their research to attract faculty, students, or external funding.  
2756 Some universities also patent the discoveries of their staff. Institutional conflicts of interest can  
2757 also arise when a research centre derives substantial support (perhaps covering years of  
2758 funding) from a single sponsor or a handful of sponsors.

2759

2760 3) *Research ethics committees.* Researchers often serve as members of research ethics  
2761 committees and conflicts of interest can arise in this role. For example, a researcher may submit  
2762 her own study protocol for review, or she may be reviewing the work of colleagues whom she  
2763 knows personally, or whose work she considers critical for the success of her institution.



2764 Research ethics committees may also have financial interests when they are directly funded by  
2765 sponsors or serve an institution that significantly depends on support from a single sponsor or  
2766 several sponsors.

2767  
2768 The fact that a research ethics committee (or the institution where it operates) is paid a fee for  
2769 reviewing a study does not present an inherent conflict of interest, provided that the fee is  
2770 established by a general policy, reasonably related to the costs of conducting the review and is  
2771 not dependent on the outcome of the review (see guideline 23 on research ethics committees).

2772  
2773 In order to evaluate the seriousness of a conflict of interest, and to determine appropriate measures for  
2774 its management, research ethics committees need to judge the risk that a secondary interest of one or  
2775 more stakeholders in a study unduly compromises or undermines its ethical conduct. This involves  
2776 judging both the likelihood that a secondary interest might compromise the rights or welfare of  
2777 participants or the scientific validity of the research, as well as judging the magnitude of the secondary  
2778 interest relative to the stakeholder's personal situation. For example, an early-career researcher with a  
2779 modest salary might have more significant academic and financial conflicts of interest than an established  
2780 senior member of the research team. Research ethics committees will have to exercise their judgment  
2781 when evaluating the seriousness of conflicts of interest. As a general rule, a serious conflict of interest  
2782 exists when there is a significant likelihood that a professional, academic, or financial interests will result  
2783 in biased study results or cause important harm or wrong to participants.

2784

2785 Of note, conflicts of interests can influence stakeholders in the research subconsciously. For example, a  
2786 researcher with a financial stake in a study may not intentionally manipulate his/her research findings.  
2787 However, his/her financial interests may subconsciously influence her analysis and interpretation of the  
2788 research data.

2789 *Management of conflicts of interest.* All stakeholders in research share responsibility for developing and  
2790 implementing policies and procedures to identify, mitigate, eliminate, or otherwise manage conflicts of  
2791 interest. Although a joint responsibility, research institutions play a critical role in creating an institutional  
2792 culture that takes conflicts of interest seriously and adopts appropriate measures for their management.  
2793 Measures for managing conflicts of interest must be proportionate to their seriousness. For example, a  
2794 minor conflict of interest may be appropriately managed by disclosure, while a serious conflict can, in rare  
2795 cases, justify excluding a researcher from the study team. Policies and measures for managing conflicts  
2796 of interest must be transparent and actively communicated to those affected.

2797

- 2798 1) *Education of researchers and research ethics committees.* Raising awareness of conflicts of  
2799 interest, as well as the importance of managing such conflicts, is essential for effective conflict of  
2800 interest procedures and policies.  
2801
- 2802 2) *Disclosure of interests to research ethics committees.* Researchers must disclose conflicts of  
2803 interest on their part to the ethical review committee or to other institutional committees designed  
2804 to evaluate and manage such conflicts. Researchers will most likely come to recognize conflicts  
2805 of interest if they are prompted to scrutinize these conflicts as an expected part of preparing a  
2806 description of their projects for ethical review. Thus, the development of a standardized  
2807 disclosure form and related educational and explanatory materials (by a committee or group of  
2808 committees, such as a research ethics association) is recommended to ensure that researchers  
2809 understand conflicts of interest and routinely report relevant facts about their own studies to  
2810 research ethics committees. It is important that disclosure forms provide a definition of conflicts of  
2811 interest and help researchers to understand that a conflict of interest is not necessarily

2812 disqualifying, but may be managed. When research ethics committees have credible evidence  
2813 about serious conflicts of interest related to a study that are not disclosed in the protocol,  
2814 research ethics committees should contact the principal researcher for further information.

2815  
2816

2817 3) *Disclosure of interests to participants.* Researchers may propose, and research ethics  
2818 committees may require, managing conflicts of interest by disclosing them to potential study  
2819 participants in the informed consent discussion and documents (for example stock ownership).  
2820 The disclosure must allow potential participants to judge the seriousness of the conflict of  
2821 interest. This goes beyond describing “the nature and sources of funding for the research”, which  
2822 is an element of informed consent (see Appendix xxx). In the case of serious conflicts of interest,  
2823 studies suggest that disclosure works best when it is provided by a health professional that is  
2824 independent of the study team and potential participants are given time to reflect.

2825  
2826

2827 4) *Mitigation of conflicts.* Research ethics committees may consider a range of other measures to  
2828 mitigate or manage conflicts of interest beyond disclosing these conflicts to potential participants.  
2829 For example, where appropriate, research ethics committees may require a member of the study  
2830 team who has no leading role in its design to obtain the informed consent of potential  
2831 participants. Research ethics committees may also require limiting the involvement of  
2832 researchers in a study when they have a serious conflict of interest. For instance, a researcher  
2833 with a serious conflict may only be involved as a consultant for specific tasks that require her  
2834 expertise, but not as a principal researcher or co-researcher. Alternatively, research ethics  
2835 committees may require independent monitoring and review of studies where, for reasons of  
2836 expertise, the full involvement of researchers with a serious conflict of interest is necessary. In  
2837 cases where a serious conflict of interest cannot be adequately mitigated, research ethics  
2838 committees may decide not to approve a study. Research ethics committees themselves must  
2839 employ similar measures to identify, mitigate and manage the conflicts of interests of their own  
2840 members. When necessary, research ethics committees may require members with a serious  
2841 conflict to withdraw from deliberations of the research ethics committee and its decisions (see  
2842 guideline 23 on research ethics committees).

2843 See also guideline 4: *potential benefits and risks*, guideline 8 on *collaborative partnership*, guideline 9:  
2844 *individual informed consent*; guideline 23 on *research ethics committees and review* and guideline 24 on  
2845 *public accountability*