

International Ethical Guidelines for Epidemiological Studies

Prepared by the
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The updating process, which began in 2003, was initiated by the CIOMS Secretariat by requesting a number of experts and institutions involved in the formulation of the 1991 CIOMS *International Guidelines for Ethical Review of Epidemiological Studies* to list new and additional topics to be covered in the updated version. Subsequently, drafting was carried out initially by an established Core Group of experts listed in Appendix 4, supported by Professor Juhana E. Idänpään-Heikkilä, then CIOMS Secretary-General, and Mr. Sev Fluss, Senior Adviser of CIOMS and chaired by Professor Michel Vallotton, Swiss Academy of Medical Sciences and President of CIOMS. The task of finalizing the various drafts was led by Professor Alexander Capron, Professor of Law and Medicine, University of Southern California, Los Angeles, California, USA as Principal Rapporteur, assisted by Professor Rodolfo Saracci, Director of Research in Epidemiology, National Research Council, Pisa, Italy and Professor Idänpään-Heikkilä and the CIOMS Secretariat. A consultation was held on the draft Guidelines in June 2007; the participants are listed in Appendix 5. The interest and comments of the many organizations and individuals who responded to the drafts of the Guidelines posted until now on the CIOMS website or otherwise made available are gratefully acknowledged (Appendix 5). A further meeting of the Core Group was held in November 2007 to incorporate the suggestions of the consultants and other comments on the pre-final draft to be posted again in February 2008 on the CIOMS website.

BACKGROUND

34

35

36 The Council for International Organizations of Medical Sciences (CIOMS) is an
37 international non-governmental organization in official relations with the World
38 Health Organization (WHO). It was founded under the auspices of WHO and the
39 United Nations Educational, Scientific and Cultural Organization (UNESCO) in
40 1949; among its mandates is to maintain collaborative relations between national and
41 international medical and scientific groups and the United Nations and its specialized
42 agencies, particularly UNESCO and WHO.

43 In the late 1970s, CIOMS began working in collaboration with WHO on ethics
44 in relation to research. The initial objective was to prepare guidelines to indicate how
45 the ethical principles that should govern the conduct of biomedical research involving
46 human subjects, as set forth in the Declaration of Helsinki (first issued by the World
47 Medical Association in 1964 and amended in 1975), could be effectively applied,
48 particularly in developing countries, given their socioeconomic circumstances, laws
49 and regulations, and executive and administrative arrangements. The first product of
50 this CIOMS/WHO undertaking was the publication in 1982 of *Proposed International*
51 *Ethical Guidelines for Biomedical Research Involving Human Subjects*.

52 The period that followed saw rapid advances in medicine and biotechnology, the
53 growth of multinational clinical trials and of research involving children and other
54 vulnerable groups, a shift in attitudes towards regarding human subjects research as
55 largely beneficial rather than threatening, and the outbreak of the HIV/AIDS
56 pandemic. These developments raised new ethical issues not considered in the
57 preparation of *Proposed Guidelines*. Moreover, the Declaration of Helsinki was again
58 twice revised (in 1983 and 1989). It therefore was timely to revise and update the
59 1982 guidelines, and CIOMS, with the cooperation of WHO and its Global
60 Programme on AIDS, in 1993 issued *International Ethical Guidelines for Biomedical*
61 *Research Involving Human Subjects*.

62 During this period, CIOMS and its collaborators also recognized that ethical
63 guidance was also needed for public health research. Therefore, even before the
64 revision of the biomedical research guidelines was completed, *International*
65 *Guidelines for Ethical Review of Epidemiological Studies* were published in 1991.

66 In the years that followed, it became apparent that the biomedical guidelines
67 would need to be revised again to address additional issues, especially those arising in
68 controlled clinical trials carried out in low-resource countries by sponsors from richer
69 countries. The updating, which was also necessitated by a major revision in the
70 Declaration of Helsinki in 2000, resulted in the publication by CIOMS and WHO of
71 revised *International Ethical Guidelines for Biomedical Research Involving Human*
72 *Subjects* in 2002. Like the 1982 and 1993 versions, the new document was designed
73 to be of use, particularly to low-resource countries, in defining national policies on the
74 ethics of biomedical research (and particularly clinical trials of pharmaceuticals),
75 applying ethical standards in local circumstances, and establishing or redefining
76 adequate mechanisms for ethical review of research involving human subjects.

77 The process of revising the research guidelines that began in the late 1990s
78 made clear that developments in the ethical analysis of all types of research using
79 human subjects had potential implications for the 1991 Guidelines for
80 epidemiological studies. Furthermore, the growing recognition of the importance of
81 epidemiological research to improving the health of the public highlighted the
82 importance of bringing the 1991 guidelines into line with current thinking on ethics
83 and human rights. Therefore, in 2003 CIOMS constituted a core group to consider
84 how the existing ethical guidance for epidemiological studies should be updated. The
85 group initially attempted to make changes in the 1991 document, but then put aside
86 that draft because of the response from persons involved in ethical review committees
87 that they found it difficult to relate the epidemiological guidelines to CIOMS 2002
88 *International Ethical Guidelines for Biomedical Research*. The group recognized
89 how widely the latter document has been disseminated, so that it is now the basic
90 conceptual and practical guide when research undergoes ethical review in institutions
91 around the world, particularly in developing countries. Intending to ensure that
92 ethical principles are consistently applied to all types of research, the core group
93 decided to prepare a Supplement to the 2002 document that would address the special
94 features of epidemiological studies. The group thereby meant to connect the ethics of
95 epidemiological research with the standards and analysis that have been developed for
96 other types of research involving human subjects and to ease the process of review
97 because many of those using the proposed supplement—especially members of, and

98 administrators for, ethical review committees—would have experience with using the
99 2002 *Guidelines* in the context of biomedical research projects.

100 In February 2006, a draft of the supplement was posted on the CIOMS website
101 and opened to comment from interested parties. The response from groups and
102 individuals involved in biomedical research was largely positive, but the same was
103 not true among epidemiologists. Some accepted the drafters' insistence that the
104 manner of presentation did not signify that the field of epidemiology should be
105 regarded as derivative from or secondary to clinical research. (Quite the contrary, as
106 the drafters noted: the field of epidemiology predates many of the methods now used
107 in clinical research.) But many objected that epidemiologists were not necessarily
108 conversant with the 2002 *Guidelines* and would therefore find it burdensome to have
109 to switch back and forth between the epidemiology supplement and the biomedical
110 research document. They were also concerned that the supplement would not
111 provoke ethical review committees that principally review biomedical research to
112 sufficiently adjust their expectations—and also their membership—to take account of
113 important differences raised by epidemiological studies. At the same time, the critics
114 also stated that ethical review committees that mostly review public health research
115 and other epidemiological studies would find it simpler to have a stand-alone set of
116 guidelines.

117 A second issue, concerning the scope of the new guidance document for
118 epidemiological research, also emerged from the comments on the 2006 draft. In
119 conducting some studies, epidemiologists alter the physical, chemical, social or
120 psychological conditions to which members of a population are exposed. Such
121 population trials resemble the clinical trials of new drugs and devices that are the
122 principal focus of the 2002 CIOMS *International Ethical Guidelines* except that
123 sometimes the unit of study is not an individual person but a community or other
124 group. It would therefore be possible for those interventional or experimental
125 epidemiological studies to be designed and reviewed under the 2002 document, and to
126 restrict the current guidelines to the unique features of observational epidemiological
127 studies. But such an approach would have several disadvantages.

128 First, while the CIOMS 2002 guidelines are familiar to many ethical review
129 committees, some committees that only review epidemiological studies may not be
130 familiar with them. These committees would be better served by a single booklet that

131 addresses both observational and interventional epidemiology. Likewise,
132 epidemiologists, who may move from conducting an observational study to an
133 interventional study, should not have to shift back and forth between one document
134 and the other. Therefore, it is the intention of the core group that this guidance
135 document encompass all types of epidemiological studies.

136 In the case of interventional studies, the present Guidelines are generally the
137 same as those in the 2002 document,¹ but whenever appropriate the commentary has
138 been focused on issues that arise in epidemiological rather than biomedical research.
139 For example, in biomedical research the focus of protection is typically on avoiding
140 physical or psychological harm; in the context of international studies, attention has
141 often been directed towards the responsibilities of commercial sponsors of research
142 from high-resource countries when they test their products in low-resource countries.
143 In epidemiological research, the sponsors are more likely to be public agencies than
144 commercial companies and the risks are more likely to involve socioeconomic harm
145 (such as through dissemination of private information) rather than physical injury. Of
146 course, some epidemiological research does utilize biomedical interventions (such as
147 vaccines) in one or more population groups, where the risk can be physical as well as
148 social. And even observational studies can involve physical risks, if the failure to
149 change conditions means that some of the subjects of a study are exposed to avoidable
150 risks of harm. Indeed, one of the most infamous cases of unethical research in the
151 Twentieth Century, the so-called Tuskegee Syphilis Study, involved the observation
152 of untreated disease in a group of poor African-Americans in rural Alabama over a
153 forty-year period; the fact that the subjects were unaware of their diagnosis and of the
154 purpose for the public health officials' interest in them and were not offered treatment
155 when antibiotics became generally available caused a scandal that propelled the
156 development of formal rules for research with human beings in the United States.

157 The present Guidelines address observational studies by noting, in the
158 commentary, the ways in which it may be appropriate to treat such research
159 differently than interventional studies (for example, regarding informed consent).
160

¹ Small changes have been made in the wording of Guidelines where this was necessary in light of differences between biomedical and epidemiological research, and three Guidelines (22-24) have been added in the present document; they are not, however, narrowly concerned with epidemiological research and are considered appropriate for inclusion in CIOMS's next edition of the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

INTRODUCTION

161

162

163 “Epidemiology is the study of the distribution and determinants of health-related
164 states or events in specified populations, and the application of this study to control of
165 health problems.” (John Last, *Dictionary of Epidemiology*, 4th edition) This volume
166 sets forth ethical guidance regarding the first part of this definition, namely, how
167 epidemiologists—as well as those who sponsor, review, or participate in the studies
168 they conduct—should identify and respond to the ethical issues that are raised by the
169 process of producing this information.

170 Epidemiology has made essential contributions to the improvement in human
171 health achieved over the past century. It can be reasonably expected that the field will
172 continue to do so by using ever more powerful and sophisticated scientific tools to
173 increase the understanding of the distribution of health and illness and of their many
174 physical, chemical, biological, behavioural, social and environmental determinants.
175 Indeed, further improving the health of the public depends on making greater use of
176 the tools of epidemiology. At the same time, it is essential that this new knowledge,
177 and the changes for the good that it prompts, be derived from studies conducted
178 according to recognized ethical standards. By focusing on the distinctive aspects of
179 epidemiological research, this document aims to provide the field with just such a set
180 of ethical standards.

181 Epidemiological research today encompasses a wide spectrum of research
182 ranging from the investigation of disease causation using the tools of molecular
183 biology in populations to the evaluation of health services and from analysis of the
184 social factors conditioning health and disease to large-scale studies of new public
185 health interventions to prevent disease. All aspects of health when studied at the level
186 of the population are the proper domain of epidemiology, which also provides
187 essential inputs for clinicians, policymakers and social analysts, for example on
188 disease frequency or on the effects of different interventions to control a disease.

189 In epidemiology, the term "studies" encompasses both routine applications of
190 epidemiological methods—for example, in public health surveillance or hospital
191 quality evaluation—and investigations designed to produce new scientific knowledge
192 and theories; the latter are addressed in the present Guidelines and commentaries. The
193 text adopts the usage common in biomedical research, in which the term "study" is

194 used—along with "investigation" or "trial"—to designate research activities; thus in
195 what follows, references to "epidemiological studies" denote epidemiological research
196 rather than practice.

197

198 *Research and practice.* In order to avoid imposing on the ordinary practice of
199 medicine all the rules and procedures created over the past six decades to protect
200 research subjects, it is conventional to define "research" as involving activities that
201 are designed to develop or contribute to generalizable knowledge. Generalizable
202 knowledge consists of theories, principles or relationships, or the accumulation of
203 information on which they are based, that can be corroborated by accepted scientific
204 methods of observation and inference. In contrast, when a physician or psychologist
205 varies conventional treatment in an attempt to produce a better result for a patient, one
206 might say that he or she was "experimenting" but since such individualized variations
207 do not produce generalizable knowledge, the activity would be regarded as practice
208 not research.

209 The "generalizable knowledge" definition works well for medical and
210 behavioural studies pertaining to human health, which are commonly denominated
211 "biomedical research" to indicate its relation to health. But the definition works less
212 well in separating practice from research in the field of epidemiology. Many studies
213 using the tools of epidemiology which are performed on a regular basis by public
214 health agencies, such as routine surveillance for disease outbreaks, are correctly
215 viewed as "practice" even though the information produced may contribute to
216 generalizable knowledge. Thus, in carrying out their activities epidemiologists (and
217 others examining the activities) need to apply careful judgment to determine whether
218 the activity should be classified as research or practice. Of course, as explained more
219 fully in these Guidelines, it does not necessarily follow that everything placed in the
220 former category is problematic or is even subject to all the requirements for advance
221 approval and individualized informed consent usually associated with research.
222 Conversely, some activities that are routinely carried out by epidemiologists do raise
223 ethical issues that may benefit from careful scrutiny or even reconsideration, even if
224 they have long traditions and are sanctioned by regulations or statutes.

225 *Ethics and epidemiology.* Progress in medical care and disease prevention
226 depends upon an understanding not only of physiological and pathological processes

227 but also of the social, cultural, economic, and other environmental determinants of
228 health, including the effects of the health-care system and other social institutions.
229 Producing that understanding requires performing research involving human subjects.
230 Such research should be carried out only by, or strictly supervised by, suitably
231 qualified and experienced investigators under accepted ethical guidelines.

232 Ethical guidelines assist both investigators and ethical review committees in
233 acting responsibly. Investigators, with whom rests the primary duty to protect the
234 rights and welfare of research subjects and to ensure the scientific quality of research,
235 can benefit through better design and administration of their protocols, including the
236 processes for obtaining consent and communicating their research findings, while
237 ethical review committees can benefit through improved evaluation and oversight of
238 studies. In their respective roles, each has a duty to see that research plans are
239 transparent, that subjects' data and biological samples are actually used for valid
240 studies, that study results are made publicly available, and that unnecessary
241 administrative obstacles to research—should they occur—are effectively removed.

242 Because of their merely observational nature, epidemiological studies in the past
243 were widely regarded as not raising any significant ethical issues and were commonly
244 carried out without approval of an ethical review committee. However, recent years
245 have brought increased attention to the ethical conduct of research generally, greater
246 awareness of the potential harms to research subjects including non-physical harm
247 from disclosures of health-related information and hence increased efforts to protect
248 privacy. All of these have implications for observational epidemiological research.
249 Investigators and review committees need to take differences between interventional
250 and observational studies into consideration in designing and approving observational
251 studies. In some cases, the differences can simplify the ethical review process; in
252 others, additional considerations are raised.

253 The mere formulation of ethical guidelines for epidemiological research
254 involving human subjects will hardly resolve all the moral doubts that can arise in
255 association with such research. Nonetheless, the present Guidelines are intended at
256 least to draw the attention of investigators, sponsors and ethical review committees to
257 the need to consider carefully the ethical implications of research protocols and the
258 manner in which research is conducted, and thus to conduce to high scientific and
259 ethical standards in epidemiological research.

INTERNATIONAL INSTRUMENTS AND GUIDELINES

260

261

262 The first official international statement on the ethics of medical research was
263 promulgated in 1947 as part of the judgment of the court in Nuremberg that tried the
264 Nazi physicians who had conducted atrocious experiments on unconsenting prisoners
265 and detainees during the Second World War. The judges set forth ten conditions—
266 which became known as the Nuremberg Code—for the ethical conduct of research
267 involving human subjects, emphasizing the necessity of voluntary consent.

268 The Universal Declaration of Human Rights, adopted by the United Nations
269 General Assembly in 1948 in the wake of the judgment in *The Doctors' Case*, states
270 that "No one shall be subjected . . . to cruel, inhuman or degrading treatment or
271 punishment" (Article 5). The International Covenant on Civil and Political Rights,
272 approved by the General Assembly in 1966 to give the Declaration legal as well as
273 moral force, explicates that this prohibition means that "In particular, no one shall be
274 subjected without his free consent to medical or scientific experimentation." (Article
275 7). (Many countries have incorporated this provision or its equivalent into their
276 constitution or public health laws and regulations.) Subsequent human rights
277 instruments, which provide special protection to women (Convention on the
278 Elimination of All Forms of Discrimination Against Women) and children
279 (Convention on the Rights of the Child), reinforce the connection between human
280 rights and the ethical principles that underlie a number of international guidelines for
281 research with human beings.

282 The most prominent of these began taking shape in the 1950s, when the World
283 Medical Association (WMA) began the process of articulating a set of duties for
284 physicians conducting medical research. Though it drew on the Nuremberg Code, the
285 WMA wanted a set of standards that was generated by the profession itself (free of
286 any association with the wartime physician-criminals) and that encompassed research
287 undertaken in the course of medical care. The resulting declaration, adopted at the
288 WMA meeting in Helsinki in 1964, became a fundamental document in the field of
289 research ethics and has influenced the formulation of international, regional and
290 national legislation and codes of conduct. The Declaration, which has been amended
291 several times, most recently in 2000 (Appendix 3), is a comprehensive international
292 statement of the ethics of research involving human subjects. It sets out ethical

293 guidelines for physicians engaged in both clinical and nonclinical biomedical
294 research.

295 Since the publication of the CIOMS 1993 Guidelines, several international
296 organizations have issued ethical guidance on clinical trials. These have included,
297 from the World Health Organization, in 1995, *Guidelines for Good Clinical Practice*
298 *for Trials on Pharmaceutical Products*; and from the International Conference on
299 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for
300 Human Use (ICH), in 1996, *Guideline on Good Clinical Practice*, designed to ensure
301 that data generated from clinical trials are mutually acceptable to regulatory
302 authorities in the European Union, Japan and the United States of America. The Joint
303 United Nations Programme on HIV/AIDS published in 2000 the UNAIDS Guidance
304 Document *Ethical Considerations in HIV Preventive Vaccine Research*; a revised
305 version, *Ethical Considerations in Biomedical HIV Prevention Trials*, was produced
306 by UNAIDS and WHO in 2007.

307 In 2001 the Council of Ministers of the European Union adopted a Directive on
308 clinical trials, which became binding in law in the countries of the Union in 2004. The
309 Council of Europe, with more than 40 Member States, has approved a Protocol on
310 Biomedical Research (which was opened for ratification by Member States on 25
311 January 2005) to implement the provisions of its 1997 Convention on Human Rights
312 and Biomedicine that relate to biomedical research.

313

GENERAL ETHICAL PRINCIPLES

314

315

316 All research involving human subjects should be conducted in accordance with
317 three basic ethical principles, namely respect for persons, beneficence and justice. It is
318 generally agreed that these principles, which in the abstract have equal moral force,
319 guide the conscientious preparation of proposals for scientific studies. In varying
320 circumstances they may be expressed differently and given different moral weight,
321 and their application may lead to different decisions or courses of action. The present
322 guidelines are directed at the application of these principles to research involving
323 human subjects.

324

325 ***Respect for persons*** incorporates at least two fundamental ethical
326 considerations, namely:

- 327 a) respect for autonomy, which requires that those who are capable of
328 deliberation about their personal choices should be treated with respect for their
329 capacity for self-determination; and
330 b) protection of persons with impaired or diminished autonomy, which requires
331 that those who are dependent or vulnerable be afforded security against harm or
332 abuse.

333

334 ***Beneficence*** refers to the ethical obligation to maximize benefits and to
335 minimize harms. This principle gives rise to norms requiring that the risks of research
336 be reasonable in the light of the expected benefits, that the research design be sound,
337 and that the investigators be competent both to conduct the research and to safeguard
338 the welfare of the research subjects. Beneficence further proscribes the deliberate
339 infliction of harm on persons; this aspect of beneficence is sometimes expressed as a
340 separate principle, ***nonmaleficence*** (do no harm).

341

342 ***Justice*** refers to the ethical obligation to treat each person in accordance with
343 what is morally right and proper, to give each person what is due to him or her. In the
344 ethics of research involving human subjects the principle refers primarily to
345 ***distributive justice***, which requires the equitable distribution of both the burdens and
346 the benefits of participation in research. Differences in distribution of burdens and

347 benefits are justifiable only if they are based on morally relevant distinctions between
348 persons; one such distinction is vulnerability. "Vulnerability" refers to a substantial
349 incapacity to protect one's own interests owing to such impediments as lack of
350 capability to give informed consent, lack of alternative means of obtaining medical
351 care or other expensive necessities, or being a junior or subordinate member of a
352 hierarchical group. Accordingly, special provision must be made for the protection of
353 the rights and welfare of vulnerable persons.

354 Sponsors of research or investigators cannot, in general, be held accountable for
355 unjust conditions where the research is conducted, but they must refrain from
356 practices that are likely to worsen unjust conditions or contribute to new inequities.
357 Neither should they take advantage of the relative inability of low-resource countries
358 or vulnerable populations to protect their own interests, by conducting research
359 inexpensively and avoiding complex regulatory systems of industrialized countries in
360 order to develop products for the lucrative markets of those countries.

361 In general, the research project should leave low-resource countries or
362 communities better off than previously or, at least, no worse off. It should be
363 responsive to their health needs and priorities in that any product developed is made
364 reasonably available to them, and as far as possible leave the population in a better
365 position to obtain effective health care and protect its own health.

366 Justice requires also that the research be responsive to the health conditions or
367 needs of vulnerable subjects. The subjects selected should be the least vulnerable
368 necessary to accomplish the purposes of the research. Risk to vulnerable subjects is
369 most easily justified when it arises from interventions or procedures that hold out for
370 them the prospect of direct health-related benefit. Risk that does not hold out such
371 prospect must be justified by the anticipated benefit to the population of which the
372 individual research subject is representative.

373 An issue, mainly for those countries and perhaps less pertinent now than in the
374 past, has been the extent to which ethical principles are considered universal or as
375 culturally relative – the universalist versus the pluralist view. The challenge to
376 international research ethics is to apply universal ethical principles to biomedical
377 research in a multicultural world with a multiplicity of health-care systems and
378 considerable variation in standards of health care. The Guidelines take the position
379 that research involving human subjects must not violate any universally applicable

380 ethical standards, but acknowledge that, in superficial aspects, the application of the
381 ethical principles, e.g., in relation to individual autonomy and informed consent,
382 needs to take account of cultural values, while respecting absolutely the ethical
383 standards.

384 Finally, it is important to remember the basic distinction between legal norms
385 and ethical norms. While the former are founded on the latter, there is no necessary
386 one-to-one correspondence between each legal and ethical norm. A law may be
387 regarded as unethical by some people (e.g., a law prescribing the death penalty for
388 certain crimes) and likewise, an ethical norm may be regarded as unlawful in a
389 country (e.g., one involving female genital mutilation). Thus it cannot be expected
390 that ethical guidelines, which translate ethical principles into the form of
391 recommendations (rather than of strict norms), will always coincide with legal
392 prescriptions. This applies all the more to international guidelines which are issued in
393 the context of legal dispositions varying from one country to another.

394

THE GUIDELINES

Guideline 1

Ethical justification and scientific validity of epidemiological research involving human beings

The ethical justification of epidemiological research involving human subjects is the prospect of discovering new ways of improving the health of individuals, groups and populations. Such research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, research subjects and that are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.

Commentary on Guideline 1

General considerations. Among the essential features of ethically justified research involving human subjects, including research with identifiable human tissue or data, are that the research offers a means of developing information not otherwise obtainable, that the design of the research is scientifically sound, and that the investigators and other research personnel are competent. The methods to be used should be appropriate to the objectives of the research and the field of study. Investigators and sponsors must also ensure that all who participate in the conduct of the research are qualified by virtue of their education and experience to perform competently in their roles. These considerations should be adequately reflected in the research protocol submitted for review and clearance (Appendix 2 specifies the items to be included in a protocol, when relevant). Scientific review is discussed further in the Commentaries to Guidelines 2 and 3: *Ethical review committees* and *Ethical review of externally sponsored research*. Other ethical aspects of research are discussed in the remaining guidelines and their commentaries.

428

429 *Observational studies.* While observational research normally does not pose a risk of
430 physical harm to individuals, this is not always the case, for several reasons. First, in
431 some non-experimental studies researchers intervene physically with subjects, such as
432 by taking blood or tissue samples. Second, even when an observational study
433 involves only questionnaires or record-examination, subjects may be at risk of
434 physical or psychological harm. For example, interviewing women in a study of
435 domestic violence may expose them to the risk of further violence. A risk of
436 psychological harm may be present when sensitive questions are asked, for instance
437 asking parents about events surrounding a child's death, or details about sexual habits.
438 Likewise, initiating research on workplace hazards may cause anxiety among both
439 employees and employers. Even research limited to an examination of existing
440 records may entail a risk for the group under investigation (such as stigmatization) or,
441 without causing measurable harm, it may still wrong people by making use of
442 information that they regard as private. Careful planning, open discussions with all
443 concerned parties (such as representatives of workers and managers in occupational
444 health research), vigorous efforts to protect confidential data, and pooling data to
445 larger entities are all part of good study design.

446

447 ***Guideline 2***

448 ***Ethical review committees***

449

450 **All proposals to conduct epidemiological research involving human subjects**
451 **must be submitted for review of their scientific merit and ethical acceptability**
452 **to one or more scientific review and ethical review committees. The review**
453 **committees must be independent of the research team, and any direct financial**
454 **or other material benefit they may derive from the research should not be**
455 **contingent on the outcome of their review. The investigator must obtain their**
456 **approval or clearance before undertaking the research. The ethical review**
457 **committee should conduct further reviews as necessary in the course of the**
458 **research, including monitoring the progress of the study.**

459

460 ***Commentary on Guideline 2***

461

462 *Inclusion in, or exemption from, review.* Research involves human subjects when an
463 investigator will directly obtain information from individuals or groups or will
464 otherwise acquire identifiable private information about them. Proposals for
465 epidemiological studies, like other research with human subjects, must usually
466 undergo prior scientific and ethical review, although some observational studies, such
467 as those utilizing publicly available or anonymous data, may not be subject to prior
468 review and approval by an ethical review committee under the regulations of the local
469 jurisdiction. When in doubt about whether or not a study involves elements that
470 warrant ethical review, epidemiologists are encouraged to consult the ethical review
471 committee or to submit their studies for review. For example, a study of sensitive
472 topics or behavior (illicit drug use; domestic violence; etc.) may merit review because
473 of its potential effects on a community or group even if the data were to be recorded
474 anonymously. Even when an exemption is claimed, the research protocol should
475 provide justification for the claimed exemption. A public health study not submitted
476 to an ethical review committee should receive administrative confirmation by a
477 competent authority that the study is exempt from review. Epidemiologists should
478 keep in mind that scientific journals generally require that papers submitted for
479 publication have received prior review by an ethical review committee.

480

481 *General observations.* Ethical and scientific review committees may function at the
482 institutional, local, regional, or national level, and in some cases at the international
483 level. The regulatory or other governmental authorities concerned should promote
484 uniform standards across committees within a country, and, under all systems,
485 sponsors of research and institutions in which the investigators are employed should
486 allocate sufficient resources to the review process. Review committees may receive
487 money for the activity of reviewing protocols, but under no circumstances may
488 payment be conditioned on a review committee's approval or clearance of a protocol.

489

490 *Scientific review.* Scientific review and ethical review are intertwined: scientifically
491 unsound research involving humans as subjects is *ipso facto* unethical in that it may
492 expose them to risk or inconvenience to no purpose; even if there is no risk of injury,
493 the wasting of subjects' and researchers' time in unproductive activities represents

494 loss of a valuable resource. Epidemiological research involving humans must conform
495 to generally accepted scientific principles, and be based on a thorough knowledge of
496 the scientific literature and other relevant sources of information, as well as adequate
497 preparatory studies. Scientific review must consider, *inter alia*, the study design,
498 including the provisions for avoiding or minimizing risk and for monitoring safety
499 when applicable, as well as the scientific qualifications of the investigators (including
500 education in the principles of research practice).

501

502 *Ethical review.* The ethical review committee is responsible for safeguarding the
503 rights, safety, and well-being of the research subjects. Many ethical review
504 committees consider both the scientific and the ethical aspects of proposed research;
505 when the tasks are separated, the ethical review committee must verify that another
506 competent expert body has determined that the research is scientifically sound. The
507 ethical review committee should also ensure that provisions for monitoring of data
508 and safety are in place, either through the committee itself or another body.

509

510 Once a research proposal has been found scientifically sound, the ethical review
511 committee should consider whether any known or possible risks to the subjects are
512 justified by the expected benefits, direct or indirect, and whether the proposed
513 research methods will minimize harm and maximize benefit. (See Guideline 8:
514 *Benefits, harms and risks of study participation.*) If the proposal is sound and the
515 balance of risks to anticipated benefits is reasonable, the committee should then
516 determine whether the procedures proposed for obtaining informed consent, when
517 applicable (see Guideline 4), are satisfactory and the process for selecting subjects is
518 equitable. The committee is also responsible for ensuring that all other ethical
519 concerns arising from a protocol are satisfactorily resolved both in principle and in
520 practice, for keeping records of its decisions, and for taking measures to follow up on
521 the conduct of ongoing research projects.

522

523 *National (centralized) or local review.* Ethical review committees may be created
524 under the aegis of national or local health administrations, national (or centralized)
525 research councils or other nationally representative bodies. In a highly centralized
526 administration a national, or centralized, review committee may be constituted for

527 both the scientific and the ethical review of research protocols. In countries where
528 research is not centrally administered, ethical review is more effectively and
529 conveniently undertaken at a local or regional level. The authority of a local ethical
530 review committee may be confined to a single institution (such as a hospital, research
531 institute, or university) or may extend to all institutions in which research is carried
532 out within a defined geographical area.

533 However committees are created, and however their jurisdiction is defined, they
534 should establish working rules regarding, for instance, frequency of meetings, a
535 quorum of members, decision-making procedures, and review of decisions. The rules
536 should protect the confidentiality of review-committee documents and discussions.
537 The committee should provide its rules to prospective investigators, and should also
538 never compel investigators to submit to unnecessary repetition of review.

539

540 *Committee membership.* Committees competent to review the scientific and/or ethical
541 aspects of epidemiological research proposals have competence on all relevant topics;
542 such committees must be multidisciplinary, including epidemiologists and other
543 experts in the design and analysis of population health studies. It is important that at
544 least some committee members (or experts co-opted on an *ad hoc* basis, as needed for
545 particular studies) be knowledgeable and up-to-date about statistical methods as
546 applied to epidemiology including sampling methodology in general, as well as about
547 the populations being studied in particular (e.g., concerning the existence of
548 subpopulations, social structure, hazards at work, etc.).

549 In addition to such experts, the membership should include other professionals
550 such as physicians, nurses, lawyers, ethicists and clergy, as well as lay persons
551 qualified to represent the cultural and moral values of the community and to ensure
552 that the rights of the research subjects will be respected. Lack of formal education
553 should not disqualify community members from joining in constructive discussion on
554 issues relating to the study and the application of its findings, and when illiterate
555 persons form the focus of a study they should either be considered for membership or
556 invited to have their views expressed. Committees should include both men and
557 women. A number of members should be replaced periodically, with the aim of
558 blending the advantages of experience with those of fresh perspectives.

559 Committees that often review occupational health research should include

560 workers' representatives, and those that often review research proposals directed at
561 specific diseases or impairments should invite or hear the views of individuals or
562 bodies representing patients with such diseases or impairments. Similarly, for research
563 involving such subjects as children, students, elderly persons or employees,
564 committees should invite, or solicit the views of, their representatives or advocates.

565

566 *Multi-centre research.* Some research projects are designed to be conducted in a
567 number of centres in different communities or countries. Generally, to ensure that the
568 results will be valid, the study must be conducted in an identical way at each centre.
569 Such studies include various kinds of epidemiological research and evaluations of
570 health service programmes in addition to clinical trials. In multi-centre studies, local
571 ethical or scientific review committees are not normally authorized to change
572 inclusion or exclusion criteria or to make other, similar modifications. They should be
573 fully empowered, however, to prevent a study that they believe to be unethical.
574 Moreover, changes that local review committees believe are necessary to protect the
575 research subjects should be documented and reported to the research institution or
576 sponsor responsible for the whole research programme for consideration and due
577 action, to ensure that all other subjects can be protected and that the research will be
578 valid across sites.

579 To ensure the validity of multi-centre research, any change in the protocol
580 should be made at every collaborating centre or institution, or, failing this, explicit
581 inter-centre comparability procedures must be introduced; changes made at some but
582 not all will defeat the purpose of multi-centre research. For some multi-centre studies,
583 scientific and ethical review may be facilitated by agreement among centres to accept
584 the conclusions of a single review committee; its members could include a
585 representative of the ethical review committee at each of the centres at which the
586 research is to be conducted, as well as individuals competent to conduct scientific
587 review. In other circumstances, a centralized review may be complemented by local
588 review relating to the local participating investigators and institutions. The central
589 committee can review the study from a scientific and ethical standpoint, while the
590 local committees verify the practicability of the study in their communities, including
591 the infrastructures, the state of training, and ethical considerations of local
592 significance.

593 In a large multi-centre epidemiological study, individual investigators will not
594 have authority to act independently, with regard to data analysis or to preparation and
595 publication of manuscripts, for instance. Such a trial usually has a set of committees
596 which operate under the direction of a steering committee and are responsible for such
597 functions and decisions. The function of the ethical review committee in such cases is
598 to review the relevant plans with the aim of avoiding abuses.

599

600 *Research in emergency situations.* The emerging best practice for research conducted
601 during an emergency—such as population studies of outbreaks of disease or of
602 disasters (and relief efforts)—is to establish the basic research design for various
603 categories of research prior to the emergency. Among other benefits, this permits
604 prior ethical review of at least the major features of the research design. When prior
605 review has not occurred, a review should be provided as quickly as possible. The
606 special problems in obtaining informed consent in emergencies are addressed in the
607 Commentary on Guideline 6.

608

609 *Sanctions.* Ethical review committees generally have no authority to impose sanctions
610 on researchers who violate ethical standards in the conduct of research involving
611 humans. They may, however, withdraw ethical approval of a research project if
612 judged necessary. They should be required to monitor the implementation of an
613 approved protocol and its progression, and to report to institutional or governmental
614 authorities any serious or continuing non-compliance with ethical standards as they
615 are reflected in protocols that they have approved or in the conduct of the studies.
616 Failure to submit a protocol to the committee should be considered a clear and serious
617 violation of ethical standards.

618 Sanctions imposed by governmental, institutional, professional or other
619 authorities possessing disciplinary power should be employed as a last resort.
620 Preferred methods of control include cultivation of an atmosphere of mutual trust, and
621 education and support to promote in researchers and in sponsors the capacity for
622 ethical conduct of research.

623 Should sanctions become necessary, they should be directed at the non-
624 compliant researchers or sponsors. They may include fines or suspension of eligibility
625 to receive research funding, to use investigational interventions, or to practise their

626 profession. Unless there are persuasive reasons to do otherwise, editors should refuse
627 to publish the results of research conducted unethically and retract any articles that are
628 subsequently found to contain falsified or fabricated data or to have been based on
629 unethical research. Drug regulatory authorities should consider refusal to accept
630 unethically obtained data submitted in support of an application for authorization to
631 market a product. Such sanctions, however, may deprive of benefit not only the errant
632 researcher or sponsor but also that segment of society intended to benefit from the
633 research; such possible consequences merit careful consideration.

634

635 *Potential conflicts of interest.* To maintain a review committee's independence from
636 the investigators and sponsors and to avoid conflict of interest, any member with a
637 special or particular interest in a proposal (whether direct or indirect) should not take
638 part in assessing the proposal if that interest could subvert the member's objective
639 judgment. Members of ethical review committees should be held to the same standard
640 of disclosure as scientific and medical research staff with regard to financial or other
641 interests that could be construed as conflicts of interest. A practical way of avoiding
642 such conflict of interest is for the committee to insist on a declaration of possible
643 conflict of interest by any of its members. A member who makes such a declaration
644 should then withdraw, when doing so is clearly appropriate, either at the member's
645 own discretion or at the request of the other members. Before withdrawing, the
646 member should be permitted to offer comments on the protocol or to respond to
647 questions of other members.

648 Research sponsors (whether commercial enterprises, governments, or
649 foundations) have good reasons to support studies that are ethically and scientifically
650 acceptable, but cases have arisen in which the conditions of funding may have
651 introduced bias. For example, an investigator may have little or no input into trial
652 design, limited access to the raw data, or limited participation in data interpretation, or
653 study results may not be published if they are unfavourable to the sponsor's product or
654 activity. As the persons directly responsible for their work, investigators should not
655 enter into agreements that interfere unduly with their access to the data or their ability
656 to analyse the data independently, to prepare manuscripts, or to publish them.

657 Investigators must disclose potential or apparent conflicts of interest on their
658 part to the ethical review committee or to other institutional committees designed to

659 evaluate and manage such conflicts. Guidance on mechanisms for ethical review
660 committees to deal with conflicts of interest appears in Guideline 22. (See also *Multi-*
661 *centre research*, above.)
662

663 **Guideline 3**

664 ***Ethical review of externally sponsored research***

665
666 **An external sponsoring organization and individual investigators should**
667 **submit the research protocol for ethical and scientific review in the country of**
668 **the sponsoring organization, and the ethical standards applied should be no**
669 **less stringent than they would be for research carried out in that country. The**
670 **health authorities of the host country, as well as a national or local ethical**
671 **review committee, should ensure that the proposed research is responsive to**
672 **the health needs and priorities of the host country and meets the requisite**
673 **ethical standards.**

674

675 ***Commentary on Guideline 3***

676

677 *Definition.* The term *externally sponsored research* refers to research undertaken in
678 one country (the host) but sponsored, financed, and sometimes wholly or partly
679 carried out by an external international or national organization or company with the
680 collaboration or agreement of the appropriate authorities, institutions and personnel of
681 the host country.

682

683 *Ethical and scientific review.* Committees in both the country of the sponsor and
684 the host country have responsibility for conducting scientific and ethical review, as
685 well as the authority to withhold approval of research proposals that fail to meet their
686 scientific or ethical standards. As far as possible, there must be assurance that the
687 review is independent and that there is no conflict of interest that might affect the
688 judgment of members of the review committees in relation to any aspect of the
689 research. When the external sponsor is an international organization, its review of the
690 research protocol must be in accordance with its own independent ethical-review
691 procedures and standards. Committees responsible for reviewing and approving
692 proposals for externally sponsored research should have among their members or

693 consultants persons who are thoroughly familiar with the customs and traditions of the
694 population or community concerned and sensitive to issues of human dignity.

695 Committees in the external sponsoring country or international organization
696 have a special responsibility to determine whether the scientific methods are sound
697 and suitable to the aims of the research; whether the drugs, vaccines, devices or
698 procedures to be studied meet adequate standards of safety; whether there is sound
699 justification for conducting the research in the host country rather than in the country
700 of the external sponsor or in another country; and whether the proposed research is in
701 compliance with the ethical standards of the external sponsoring country or
702 international organization.

703 Committees in the host country have a special responsibility to determine
704 whether the objectives of the research are responsive to the health needs and priorities
705 of that country. The ability to judge the ethical acceptability of various aspects of a
706 research proposal requires a thorough understanding of a community's customs and
707 traditions. The ethical review committee in the host country, therefore, must have as
708 either members or consultants persons with such understanding; it will then be in a
709 favourable position to determine the acceptability of the proposed means of obtaining
710 informed consent and otherwise respecting the rights of prospective subjects as well
711 as of the means proposed to protect the welfare of the research subjects. Such persons
712 should be able, for example, to indicate suitable members of the community to serve
713 as intermediaries between investigators and subjects, and to advise on whether
714 material benefits or inducements may be regarded as appropriate in the light of a
715 community's gift-exchange and other customs and traditions.

716 When a sponsor or investigator in one country proposes to carry out research in
717 another, the ethical review committees in the two countries may, by agreement,
718 undertake to review different aspects of the research protocol. In short, in respect of
719 host countries either with developed capacity for independent ethical review or in
720 which external sponsors and investigators are contributing substantially to developing
721 such capacity, ethical review in the external, sponsoring country may be limited to
722 ensuring compliance with broadly stated ethical standards. The ethical review
723 committee in the host country can be expected to have greater competence for
724 reviewing the detailed plans for compliance, in view of its better understanding of the
725 cultural and moral values of the population in which it is proposed to conduct the

726 research; it is also likely to be in a better position to monitor compliance in the course
727 of a study. However, in respect of research in host countries with inadequate capacity
728 for independent ethical review, full review by the ethical review committee in the
729 external sponsoring country or international agency is necessary.

730

731 *Industry-sponsored research.* In industry-sponsored research on possible occupational
732 hazards, the protection of confidential information on products and production
733 processes should be respected. Such protection should not, however, prevail over the
734 primary interests of identifying potential health effects and of communicating the
735 research results to all involved parties and to the scientific community.

736

737

Guideline 4

738

Individual informed consent

739

740 **For all epidemiological research involving humans the investigator must obtain**
741 **the voluntary informed consent of the prospective subject or, in the case of an**
742 **individual who is not capable of giving informed consent, the permission of a**
743 **legally authorized representative in accordance with applicable law. Waiver of**
744 **individual informed consent is to be regarded as exceptional, and must in all**
745 **cases be approved by an ethical review committee unless otherwise permitted**
746 **under national legislation that conforms to the ethical principles in these**
747 **Guidelines.**

748

Commentary on Guideline 4

750

751 *General considerations.* Voluntary informed consent is a decision to participate in
752 research, taken by a competent individual who has received the necessary
753 information; who has adequately understood the information; and who, after
754 considering the information, has arrived at a decision without having been subjected
755 to coercion, undue influence or inducement, or intimidation.

756

757 Informed consent is based on the principle that competent individuals are
758 entitled to choose freely whether to participate in research. Informed consent
embodies the individual's freedom of choice and respects the individual's autonomy.

759 As an additional safeguard, it must always be complemented by independent ethical
760 review of research proposals. This safeguard of independent review is particularly
761 important as many individuals are limited in their capacity to give adequate informed
762 consent; they include young children, adults with severe mental or behavioural
763 disorders, and persons who are unfamiliar with medical concepts and technology (See
764 Guidelines 13, 14 and 15).

765

766 *Process.* Obtaining informed consent is a process that is begun when initial contact is
767 made with a prospective subject and continues throughout the course of the study. By
768 informing the prospective subjects, by repetition and explanation, by answering their
769 questions as they arise, and by ensuring that each individual understands each
770 procedure, investigators elicit their informed consent and in so doing manifest respect
771 for their dignity and autonomy. Each individual must be given as much time as is
772 needed to reach a decision, including time for consultation with family members or
773 others. Adequate time and resources should be set aside for informed-consent
774 procedures.

775

776 *Language.* Informing the individual subject must not be simply a ritual recitation of
777 the contents of a written document. Rather, the investigator must convey the
778 information, whether orally or in writing, in language that suits the individual's level
779 of understanding. The investigator must bear in mind that the prospective subject's
780 ability to understand the information necessary to give informed consent depends on
781 that individual's maturity, intelligence, education and belief system. It depends also on
782 the investigator's ability and willingness to communicate with patience and
783 sensitivity.

784

785 *Comprehension.* The investigator must then ensure that the prospective subject has
786 adequately understood the information. The investigator should give each one full
787 opportunity to ask questions and should answer them honestly, promptly and
788 completely. In some instances the investigator may administer an oral or a written test
789 or otherwise determine whether the information has been adequately understood.
790 (See also Commentary on Guideline 6)

791

792 *Documentation of consent.* Consent may be indicated in a number of ways. The
793 subject may imply consent by voluntary actions, express consent orally, or sign a
794 consent form. As a general rule, the subject should sign a consent form, or, in the
795 case of incompetence, a legal guardian or other duly authorized representative should
796 do so. The ethical review committee may approve waiver of the requirement of a
797 signed consent form if the research carries no more than minimal risk—that is, risk that
798 is no more likely and not greater than that attached to routine medical or
799 psychological examination—and if the procedures to be used are only those for which
800 signed consent forms are not customarily required outside the research context. Such
801 waivers may also be approved when existence of a signed consent form would be an
802 unjustified threat to the subject's confidentiality. Particularly when the information is
803 complicated, it is usually advisable to give subjects information sheets to retain; these
804 may resemble consent forms in all respects except that subjects are not required to
805 sign them. Their wording should be cleared by the ethical review committee. When
806 consent has been obtained orally, for example in a telephone interview, investigators
807 are responsible for providing documentation or proof of consent.

808

809 *Renewing consent.* When material changes occur in the conditions or the procedures
810 of a study the investigator should once again seek informed consent from the subjects.
811 For example, when a study itself (or another source) generates new information that
812 would have to be disclosed were any subjects being newly recruited to the study,
813 existing subjects should be given such information promptly and asked whether they
814 agree to continue in the study.

815 In long-term studies involving active follow-up, subjects who do not wish to
816 continue will simply stop participating, but in studies involving only passive follow-
817 up it is appropriate to inform subjects periodically of the status of the study and to
818 seek their agreement to continue having their on-going records incorporated into the
819 data base. Prior to the initiation of such long-term studies (i.e., those lasting two or
820 more quinquennia), the plans for such re-consenting should be presented to the ethical
821 review committee responsible for reviewing and approving the study.

822

823 *Cultural considerations.* In some cultures an investigator may enter a community to
824 conduct research or approach prospective subjects for their individual consent only

825 after obtaining permission from a community leader, a council of elders, or another
826 designated authority. Such customs must be respected. In no case, however, may the
827 permission of a community leader or other authority substitute for individual
828 informed consent. (To avoid a misunderstanding, the person from whom permission is
829 sought should be informed in advance that consent will be still sought from
830 individuals enrolling in research, lest this practice be seen as unanticipated disrespect
831 for his or her authority.) In some populations the use of a number of local languages
832 may complicate the communication of information to potential subjects and the ability
833 of an investigator to ensure that they truly understand it. Many people in all cultures
834 are unfamiliar with, or do not readily understand, scientific concepts such as those of
835 placebo or randomization. Sponsors and investigators should develop culturally
836 appropriate ways to communicate information that is necessary for adherence to the
837 standard required in the informed consent process. Also, they should describe and
838 justify in the research protocol the procedure they plan to use in communicating
839 information to subjects. For collaborative research in developing countries the
840 research project should, if necessary, include the provision of resources to ensure that
841 informed consent can indeed be obtained legitimately within different linguistic and
842 cultural settings.

843

844 *Consultation with community members.* Even when individualized consent is not
845 feasible, investigators may be asked by the ethical review committee to ascertain the
846 views of representative members of the relevant community on the proposed research.
847 Consultation with the community should be sustained throughout the period of the
848 study; eliciting community concerns may require study staff to mobilize the
849 community and provide means for members to express their opinions. The opinions of
850 persons in a position equivalent to those whose biological samples or records will be
851 used in a study offer a relevant point for determining whether such a study would
852 offend community norms of privacy and autonomy. Such efforts are not the same as
853 obtaining permission from community leaders to undertake a study; rather they are
854 aimed at obtaining the views of people who are in effect proxies for the potential
855 subjects—for example, unions or other workers' organizations for studies involving
856 occupational records, associations that represent population at high risk for disease
857 (such as sex workers' groups, in the case of HIV infection), and patient organizations

858 for studies involving records or pathology specimens stored at a hospital. In designing
859 their studies, researchers should be guided by this feedback in deciding whether, or to
860 what extent, the persons whose records or specimens will be studied would be likely
861 to object to such use if it were possible to ask them individually; likewise, ethical
862 review committees may request that the researcher supply information from such
863 community consultations as a part of a research proposal to use personally identifiable
864 records or samples without individual informed consent. The process of community
865 consultation, and the justification for using it, should be specified in the protocol so
866 that the ethical review committee can evaluate what is proposed.

867

868 *Community review of, and permission for, studies.* Investigators carrying out
869 epidemiological research sometimes include a process of review by representatives of
870 the community in which it is proposed to conduct the study, particularly when the
871 research originates outside that community or even outside the country in which the
872 community is located. Such review can take the form of a "dialogue" with the
873 community about the proposed study and its potential implications, or a more
874 structured consultation that would document the concerns of a socially identifiable
875 group. In some cases, formal approval may be legally required; for example, under
876 US law, a Native American tribal council must formally approve any research
877 conducted within tribal jurisdiction. In industry-based occupational epidemiology, the
878 agreement and cooperation of employers and employees is a necessary requisite to the
879 conduct of studies. Epidemiologists should usually follow the same approach when
880 developing field investigations, especially when research findings may be presented
881 or interpreted in ways that directly relate to a community or other identifiable group
882 of people or in which the collectivity itself is the unit of analysis. Those consulted
883 should be in a position to speak on behalf of the community or to reflect its views;
884 researchers should have adequate time and resources to discern how the study
885 population is organized socially and politically and which groups can best speak with
886 authority for the population. Care should, of course, be taken to ensure that those
887 consulted include all relevant groups and do not exclude, for instance, women or
888 members of minority groups. As previously noted, plans for community review
889 should be specified in the protocol, to allow their evaluation by the ethical review
890 committee.

891

892 *Use of medical records and biological specimens collected for other purposes.*

893 People have a right to know that their medical records or biological specimens may be
894 used for research. Records and specimens taken in the course of clinical care, or for
895 an earlier study, may be used for research without the consent of the patients/subjects
896 only if an ethical review committee has determined that the research poses minimal
897 risk, that the rights or interests of the patients will not be violated, that their privacy
898 and confidentiality or anonymity are assured, and that the research is designed to
899 answer an important question and would be impracticable if the requirement for
900 informed consent were to be imposed. Appropriate standards and procedures are
901 discussed more fully in Guideline 24 and its Commentary. (See also Guideline 18)

902

903 *Waiver of consent requirements in epidemiological studies.* Investigators should not
904 initiate epidemiological research involving human subjects without first obtaining
905 each subject's informed consent, unless they have received explicit approval to do so
906 from an ethical review committee or the research activity is authorized by legislation
907 or competent authorities in accord with the ethical principles in these Guidelines.

908 Categories of epidemiological research for which consent may be waived include:

- 909 a. the use of personally non-identifiable materials;
910 b. the use of personally identifiable materials with special justification;
911 c. studies performed within the scope of regulatory authority;
912 d. studies using health-related registries that are authorized under national
913 regulations; and
914 e. cluster-randomized trials.

915 The rules and processes for waiver of consent apply also to situations in which
916 permission is obtained from appropriate surrogates for research involving subjects
917 who lack the capacity to consent for themselves (see Guidelines 14 and 15).

918

919 *a. When personally non-identifiable materials are used.* As noted under Guideline 2,
920 some epidemiological studies, for example those using publicly available data, may
921 be exempt from ethical review and, *a fortiori*, from individual informed consent. In
922 other cases, review may be appropriate but individual consent may not be relevant or
923 required. For example, the individual consent requirement does not arise when the

924 materials used in the research are not personally identifiable (meaning that, by
925 definition, the individuals concerned would be unknown to the researcher and hence
926 could not be contacted to obtain consent).

927

928 *b. When personally identifiable materials are used.* Even when a study involves data
929 or material that carry a person's name or that are linked by a code to a person, an
930 ethical review committee may approve observational research using such data or
931 material without requiring individual consent prior to the research. The committee
932 may do so if it is convinced by the protocol that (a) subjects would be exposed to no
933 more than minimal risk, and (b) either the study involves only publicly available data
934 or the requirement of individual informed consent would make the conduct of the
935 research impracticable.

936 An investigator who proposes not to seek informed consent for a non-
937 interventional study that uses personally identifiable information which is not publicly
938 available (including data derived from biological samples and medical records) must
939 justify to an ethical review committee not obtaining consent; the committee should
940 ensure that access to such information is strictly limited in time and extent for the
941 specific research purposes, that allowing the investigator to use it will not
942 compromise the interests or welfare of any persons identified by the data, that any risk
943 of harm will be minimized, that the use accords with locally applicable legal
944 requirements, and that there is no known objection of the individual to such use. (The
945 obligation of institutions to make available means for people to opt out of having their
946 stored biological material and associated records used for research is discussed in
947 Guideline 24 and the associated Commentary.)

948 The most common justification for using records or samples collected in the
949 past without consent is that it would be impracticable or prohibitively expensive to
950 locate the persons whose samples or records are to be examined; this may happen
951 when, for instance, the study involves reviewing hospital records or performing new
952 tests on blood samples collected at a time when consent to future research uses of
953 such samples was not usually sought (a point further elaborated under Guideline 24).
954 On the other hand, the reluctance of individuals to agree to participate would not
955 constitute impracticability; data from individuals who have specifically rejected such
956 uses in the past may be used only with proper, official authorization in public health

957 emergencies. (The special circumstances of consent for research under emergency
958 conditions is elaborated in the Commentary on Guideline 2.)

959 Implicit in the argument for use of personally identifiable material without
960 consent is the claim that the value of the research and the unfeasibility of obtaining
961 consent justify violating a person's interest in becoming a subject of research only
962 with his or her knowledge and agreement. Thus, the task of the ethical review
963 committee in each case is to evaluate the merits of this claim when set forth by an
964 investigator: how important is the research and could the desired information be
965 produced by another method, what would be the costs and burdens of contacting the
966 persons whose data would be used in the study, how difficult would it be to meet
967 those costs and burdens, and is the imposition of this difficulty justified by the nature
968 of the interests that would be infringed or the potential harm created by allowing the
969 investigator to proceed without consent?

970 The committee should also consider whether any mitigation—such as
971 anonymizing the data—can be undertaken without seriously compromising the
972 scientific merits of the proposed study. When research using personally identifiable
973 data from records or samples collected in the past without an appropriate consent
974 procedure is permitted without consent, the committee should ensure that the
975 investigator (and sponsor) will strictly safeguard the confidentiality of subjects. For
976 this purpose, up-to-date technical means of data encryption may be valuable for
977 safeguarding the confidentiality of records.

978 Anonymization of samples and data will also make it impossible to convey to
979 subjects any findings that might be relevant to the health of the person concerned or
980 family members. Studies that could produce such findings should always include
981 information about the circumstances, if any, under which such findings would be
982 disclosed to the persons concerned or others. It is usually acceptable not to disclose
983 such findings; indeed, it is often imprudent to convey individual findings in research
984 because the significance of the finding will not be well established and the method
985 used may not yet have met the standards used for clinically approved tests. If it is
986 determined that the research is of a sort that could produce clinically significant
987 findings, an alternative to irreversible anonymization would be to lodge the key to the
988 coding system with an independent third party who would take on the responsibility

989 of notifying the persons concerned when a specified potential hazard has been
990 identified.

991

992 *c. When studies are performed within the scope of regulatory authority.* Consent may
993 also not be required for studies that involve data not publicly available but which are
994 carried out under legislative or regulatory authority for public health, such as disease
995 surveillance. The extent and limits of such permission are a matter of local law but
996 epidemiologists must still consider whether, in a given case, it is ethical to use their
997 public authority to access personal data for research purposes. When their use of such
998 data does not clearly constitute a public health activity (e.g., when adverse reaction
999 monitoring produces findings which raise a research issue the study of which would
1000 go beyond routine surveillance), the epidemiologists should seek individual consent
1001 for the use of the data or demonstrate that the research meets one of the other
1002 conditions for waiving informed consent, as explained in this Commentary. Even
1003 when individual consent is not required, the usual expectations of risk minimization,
1004 protection of confidentiality, and compliance with all other legal requirements still
1005 apply.

1006

1007 *d. Studies using health-related registries.* The creation and maintenance of health-
1008 related registries (e.g., cancer registries, databanks of genetic and other anomalies in
1009 newborn babies, etc.) provide a major resource for many public health activities, from
1010 disease prevention to resource allocation. Several considerations support the common
1011 practice of requiring that all practitioners submit relevant data to such registries: the
1012 importance of having comprehensive information to provide accurate information
1013 about an entire population; the scientific need to include all cases in order to avoid
1014 undetectable selection bias; and the general ethical principle that burdens and benefits
1015 should be distributed equitably across the population. Hence, registries that are
1016 established or officially recognized by governmental authorities usually involve
1017 mandatory rather than voluntary collection of data.

1018 Studies using data from such registries (as well as studies that link data from
1019 several registries or that combine registry-data with information from publicly
1020 available sources) thus involve the use of data that have been compiled without the
1021 informed consent of the individuals involved. Such studies should be submitted to an

1022 ethical review committee and permission should also be sought from the competent
1023 authority that is legally responsible for the maintenance and use of the registry. When
1024 an investigator plans to contact persons based on their inclusion in the registry (e.g.,
1025 to obtain from them additional information for research purposes beyond the data
1026 supplied by the registry), the investigator should bear in mind that these persons may
1027 be unaware that their data were submitted to the registry or unfamiliar with the
1028 process by which investigators obtain access to the data. Investigators are cautioned to
1029 ensure that their access to the registry information is appropriately explained to the
1030 potential research subjects by the people who run the registry or other public
1031 authorities, preferably before the investigators approach the subjects.

1032

1033 *e. Cluster-randomized trials.* Epidemiological research can take the form of a trial in
1034 which an intervention is targeted to a whole group of people such as all the students in
1035 a school or all residents of a community, and in which the groups—rather than the
1036 individuals within the group—are randomly assigned to the different arms of the trial.
1037 Examples include a vaccination campaign applied at the school level, fluoridation of
1038 the drinking-water supply to prevent dental caries, a change in healthcare
1039 reimbursement policies, or a change in incineration practices at local waste disposal
1040 sites. In a cluster-randomized trial, individual persons usually do not have an
1041 opportunity to consent to the study itself but should typically still be made aware that
1042 it will take place. Depending upon the way the study is conducted, individuals may or
1043 may not be able to decline participation in the study. For example, parents could
1044 consent or not consent to their child's vaccination at school or a person could decide
1045 to drink bottled water rather than use water that may be fluoridated; conversely, it
1046 would be difficult for a person to change the air he or she breathed outside in a study
1047 comparing methods of incinerating waste, or for a person to move to a different
1048 jurisdiction where the experimental method for healthcare reimbursement is not being
1049 tested. As in all studies, investigators have a responsibility to describe in the protocol
1050 the information that will be provided to the decision-makers and to individuals within
1051 the clusters.

1052 In a cluster-randomized trial, the investigator should identify an appropriate
1053 person or body (e.g., a community leader, headmaster, or local health council) that has
1054 authority to give permission for the cluster to participate in the study and to be

1055 assigned on a random basis to one arm or another of the study. While this decision-
1056 maker may not have been appointed or elected for the specific purpose of giving
1057 permission for the cluster to participate in research, the scope of authority should
1058 encompass interventions of the type in question if provided outside of a research
1059 project; moreover, the decision-maker should ensure that the risks of participation in
1060 the study and the randomization are commensurate with the benefits for the cluster or
1061 for society. The decision-maker may choose to consult a wider group of community
1062 representatives or advisers before taking the decision to permit the study.

1063

1064

Guideline 5

1065

Obtaining informed consent:

1066

Essential information for prospective research subjects

1067

1068 **Before requesting an individual's consent to participate in research, the**
1069 **investigator must provide the following information, in language or another**
1070 **form of communication that the individual can understand:**

1071

1072 1) **that the individual is invited to participate in research, the**
1073 **reasons for considering the individual suitable for the research, and that**
1074 **participation is voluntary;**

1075

1076 2) **that the individual is free to refuse to participate and will be free**
1077 **to withdraw from the research at any time without penalty or loss of**
1078 **benefits to which he or she would otherwise be entitled;**

1079

1080 3) **the purpose of the research, the procedures to be carried out by**
1081 **the investigator and the subject, and an explanation of how the research**
1082 **differs from routine medical care;**

1083

1084 4) **for controlled trials, an explanation of features of the research**
1085 **design (e.g., randomization, double-blinding), and that the subject will not**
1086 **be told of the assigned treatment until the study has been completed and**
1087 **the blind has been broken;**

1088

- 1089 5) **the expected duration of the individual's participation (including**
1090 **number and duration of visits to the research centre and the total time**
1091 **involved) and the possibility of early termination of the trial or of the**
1092 **individual's participation in it;**
1093
- 1094 6) **whether money or other forms of material goods will be provided**
1095 **in return for the individual's participation and, if so, the kind and amount;**
1096
- 1097 7) **that, after the completion of the study, subjects will be informed**
1098 **of the findings of the research in general, and individual subjects will be**
1099 **informed of any finding that relates to their particular health status;**
1100
- 1101 8) **that subjects have the right of access to their data on demand,**
1102 **even if these data lack immediate clinical utility (unless the ethical review**
1103 **committee has approved temporary or permanent non-disclosure of data, in**
1104 **which case the subject should be informed of, and given, the reasons for**
1105 **such non-disclosure);**
1106
- 1107 9) **any foreseeable risks, pain or discomfort, or inconvenience to**
1108 **the individual (or others) associated with participation in the research,**
1109 **including risks to the health or well-being of a subject's spouse or partner;**
1110
- 1111 10) **the direct benefits, if any, expected to result to subjects from**
1112 **participating in the research;**
1113
- 1114 11) **the expected benefits of the research to the community or to**
1115 **society at large, or contributions to scientific knowledge;**
1116
- 1117 12) **whether, when and how any products or interventions proven by**
1118 **the research to be safe and effective will be made available to subjects after**
1119 **they have completed their participation in the research, and whether they**
1120 **will be expected to pay for them;**
1121
- 1122 13) **any currently available alternative interventions or courses of**
1123 **treatment;**
1124

1125 14) **the provisions that will be made to ensure respect for the privacy**
1126 **of subjects and for the confidentiality of records in which subjects are**
1127 **identified;**

1128

1129 15) **the limits, legal or other, to the investigators' ability to safeguard**
1130 **confidentiality, and the possible consequences of breaches of**
1131 **confidentiality;**

1132

1133 16) **policy with regard to the use of results of genetic tests and**
1134 **familial genetic information, and the precautions in place to prevent**
1135 **disclosure of the results of a subject's genetic tests to immediate family**
1136 **relatives or to others (e.g., insurance companies or employers) without the**
1137 **consent of the subject;**

1138

1139 17) **the sponsors of the research, the institutional affiliation of the**
1140 **investigators, and the nature and sources of funding for the research;**

1141

1142 18) **the possible research uses, direct or secondary, of the subject's**
1143 **medical records and of biological specimens taken in the course of clinical**
1144 **care (See also Guidelines 4 and 18 Commentaries);**

1145

1146 19) **whether it is planned that biological specimens collected in the**
1147 **research will be destroyed at its conclusion, and, if not, details about their**
1148 **storage (where, how, for how long, and final disposition) and possible**
1149 **future use, and that subjects have the right to decide about such future use,**
1150 **to refuse storage, and to have the material destroyed (See Guideline 4**
1151 **Commentary);**

1152

1153 20) **whether commercial products may be developed from biological**
1154 **specimens, and whether the participant will receive monetary or other**
1155 **benefits from the development of such products;**

1156

1157 21) **whether the investigator is serving only as an investigator or as**
1158 **both investigator and the subject's physician;**

1159

1160 22) **the extent of the investigator's responsibility to provide medical**

1161 **services to the participant;**

1162

1163 23) **that treatment will be provided free of charge for specified types**
1164 **of research-related injury or for complications associated with the**
1165 **research, the nature and duration of such care, the name of the**
1166 **organization or individual that will provide the treatment, and whether there**
1167 **is any uncertainty regarding funding of such treatment;**

1168

1169 24) **in what way, and by what organization, the subject or the**
1170 **subject's family or dependants will be compensated for disability or death**
1171 **resulting from such injury (or, when indicated, that there are no plans to**
1172 **provide such compensation);**

1173

1174 25) **whether or not, in the country in which the prospective subject**
1175 **is invited to participate in research, the right to compensation is legally**
1176 **guaranteed;**

1177

1178 26) **that an ethical review committee has approved or cleared the**
1179 **research protocol.**

1180

1181 ***Commentary on Guideline 5***

1182

1183 The points specified in this Guideline—which were developed in the context of
1184 biomedical research—are generally relevant when obtaining informed consent for
1185 interventional research (especially population studies of drugs and devices) but are
1186 not all required in most observational studies. (In particular, items 4, 12, 13, and 21-
1187 24 are unlikely to be relevant.) Depending on the specifics of the study design, the
1188 investigator will need to justify to the ethical review committee why any particular
1189 items have been omitted from the consent process; a committee may, of course,
1190 decide that the researcher should be encouraged, as a prudential matter, to include
1191 some points that are not strictly speaking required. Alternatively, an ethical review
1192 committee may wish to provide investigators with a shorter list of points to be
1193 addressed in the consent process for observational studies.

1194 Some of the points specified in this Guideline present special problems in the
1195 context of epidemiological research. The statement in Item #2 that individuals are
1196 “free to withdraw from the research at any time” rests on the principle that it is
1197 ethically unacceptable to force a person to participate in research. In epidemiological
1198 studies, a person’s “withdrawal” from research can take several forms. The first,
1199 which is a subject’s request that the gathering of new data about the subject cease
1200 (e.g., in a longitudinal study), must be honored, just as any other withdrawal from on-
1201 going participation in a study should be. The second could involve a request that the
1202 person’s data (and perhaps biological materials) be removed from a database and/or
1203 repository. Such removal may be very difficult (or impossible if the data have been
1204 anonymized), would risk undermining the validity of studies using the database, and
1205 would typically seem disproportional to the individual’s interest, since—unlike an on-
1206 going intervention study—the person does not bear any burden at present. If an
1207 investigator, with the approval of the ethical review committee, does not intend to
1208 honor requests to remove data and/or biological samples, this policy should be clearly
1209 stated in the consent document.

1210 Item #7 requires two things: that subjects as a group be informed about the
1211 general findings of a study and that individuals be informed about any test results or
1212 other findings relevant to their personal health status. As noted in the Commentary to
1213 Guideline 4, when a study employs anonymization, which makes it impossible to
1214 notify individuals (and, in some cases, even identifiable groups of subjects) of
1215 research findings or personal test results, the ethical review committee should take
1216 this into account in deciding whether to approve the study. Even when they have not
1217 anonymized the data, epidemiologists have often not notified individual subjects of
1218 test results. In light of contemporary standards for informed consent, however,
1219 epidemiologists should make subjects aware of findings that are clinically relevant to
1220 their individual health. When (e.g., because of the scale of a particular study) an
1221 investigator does not plan to do so, he or she must obtain approval from the ethical
1222 review committee. In all cases, the extent to which findings will be disclosed to
1223 subjects as a group or as individuals should be clearly conveyed in the informed
1224 consent material.

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Guideline 6

Obtaining informed consent:

Obligations of investigators and sponsors

Investigators have a duty to:

- **refrain from unjustified deception, undue influence, or intimidation;**
- **seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;**
- **when individual consent is required, obtain from each prospective subject a signed form as evidence of informed consent—investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee (See Guideline 4 Commentary, *Documentation of consent*);**
- **renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate; and,**
- **renew the informed consent of each subject in long-term studies at pre-determined intervals, even if there are no changes in the design or objectives of the research.**

The principal investigator has a non-delegable duty to ensure that all personnel working on the study comply with this Guideline.

Sponsors have a duty to ensure that these obligations are fulfilled.

Commentary on Guideline 6

1262 The investigator is responsible for ensuring the adequacy of informed consent
1263 from each subject, whether the investigator undertakes this task or delegates it to other
1264 members of the research team. The person obtaining informed consent should be
1265 knowledgeable about the research and capable of answering questions from
1266 prospective subjects. Investigators in charge of the study must make themselves
1267 available to answer questions at the request of subjects. Any restrictions on the
1268 subject's opportunity to ask questions and receive answers before or during the
1269 research undermines the validity of the informed consent.

1270

1271 *Consent by subjects enrolled by mail or electronic means.* In some epidemiological
1272 studies, no face-to-face contact occurs between investigators and subjects. For
1273 example, subjects may be asked to provide electronic authorization for the use of their
1274 personal data in a study, or subjects may be asked to complete a questionnaire over
1275 the Internet. When subjects are enrolled in such studies by mail or electronic means
1276 (e.g., e-mail, Internet, etc.), difficulties may arise in fulfilling investigators' duties to
1277 ensure that subjects are able to receive answers to any questions and to ascertain that
1278 subjects adequately understand relevant facts. Potential subjects enrolled in these
1279 ways should therefore be given a means (such as a toll-free phone number or email
1280 address) to enable them to pose questions to, and receive answers from, the research
1281 team concerning the study. Since investigators may not have direct contact, through
1282 such means of communication, with all potential subjects, it is especially important
1283 that the materials used for mail enrolment are worded carefully to maximize the
1284 chances that the subjects enrolled will have an adequate understanding of information
1285 relevant to their participation in the study. (see also Guideline 23)

1286

1287 *Withholding information and deception.* Sometimes, to ensure the validity of research,
1288 investigators withhold certain information in the consent process. For example, when
1289 tests will be performed to monitor subjects' compliance with a protocol, subjects may
1290 not be told the purpose of the testing, since if they knew their compliance was being
1291 monitored they might modify their behaviour and hence invalidate results. In most
1292 such cases, the prospective subjects are asked to consent to remain uninformed of the
1293 purpose of some procedures until the research is completed; after the conclusion of
1294 the study they are given the omitted information. More generally, when providing

1295 certain information (e.g., regarding the study hypothesis) would jeopardize the
1296 validity of the research, subjects are sometimes not even told that some information
1297 has been withheld until after the research has been completed. Any withholding of
1298 information, and the procedures used to provide information subsequently, must
1299 receive the explicit approval of the ethical review committee based on the necessity of
1300 the withholding, the minimization of attendant risks to subjects, and the adequacy of
1301 the procedures for “debriefing” subjects after their participation in the study.

1302 Active deception of subjects is considerably more controversial than simply
1303 withholding certain information. Lying to subjects is a tactic not commonly employed
1304 in biomedical research. Social and behavioural scientists, however, sometimes
1305 deliberately misinform subjects to study their attitudes and behaviour. For example,
1306 scientists have pretended to be patients to study the behaviour of health-care
1307 professionals and patients in their natural settings.

1308 Some people maintain that active deception is never permissible. Others
1309 would permit it in certain circumstances. Deception is not permissible, however, in
1310 cases in which the deception itself would disguise the possibility of the subject being
1311 exposed to more than minimal risk. When deception is deemed indispensable to the
1312 methods of a study, the investigators must demonstrate to an ethical review committee
1313 that no other research method would suffice; that significant advances could result
1314 from the research; and that nothing has been withheld that, if divulged, would cause a
1315 reasonable person to refuse to participate. The ethical review committee should
1316 determine the consequences for the subject of being deceived, and whether and how
1317 deceived subjects should be informed of the deception upon completion of the
1318 research. Such informing, commonly called “debriefing”, ordinarily entails explaining
1319 the reasons for the deception. A subject who disapproves of having been deceived
1320 should be offered an opportunity to refuse to allow the investigator to use information
1321 thus obtained. Investigators and ethical review committees should be aware that
1322 deceiving research subjects may wrong them as well as harm them; subjects may
1323 resent not having been informed when they learn that they have participated in a study
1324 under false pretences. In some studies there may be justification for deceiving persons
1325 other than the subjects by either withholding or disguising elements of information.
1326 Such tactics are often proposed, for example, for studies of the abuse of spouses or
1327 children. An ethical review committee must review and approve all proposals to

1328 deceive persons other than the subjects. Subjects are entitled to prompt and honest
1329 answers to their questions; the ethical review committee must determine for each
1330 study whether others who are to be deceived are similarly entitled.

1331

1332 *Intimidation and undue influence.* Intimidation in any form invalidates informed
1333 consent. Prospective subjects who are patients often depend for medical care upon the
1334 physician/investigator, who consequently has a certain credibility in their eyes, and
1335 whose influence over them may be considerable, particularly if the study protocol has
1336 a therapeutic component. They may fear, for example, that refusal to participate
1337 would damage the therapeutic relationship or result in the withholding of health
1338 services. The physician/investigator must assure them that their decision on whether
1339 to participate will not affect the therapeutic relationship or other benefits to which
1340 they are entitled. In this situation the ethical review committee should consider
1341 whether a neutral third party should seek informed consent.

1342 The prospective subject must not be exposed to undue influence. The borderline
1343 between justifiable persuasion and undue influence is imprecise, however. The
1344 researcher should give no unjustifiable assurances about the benefits, risks or
1345 inconveniences of the research, for example, or induce a close relative or a
1346 community leader to influence a prospective subject's decision. (See also Guideline 4:
1347 *Individual informed consent.*)

1348

1349 *Risks.* Investigators should be as objective as possible in discussing the details of the
1350 experimental intervention, the pain and discomfort that it may entail, and known risks
1351 and possible hazards. In complex research projects it may be neither feasible nor
1352 desirable to inform prospective participants fully about every possible risk. They
1353 must, however, be informed of all risks that a 'reasonable person' would consider
1354 material to making a decision about whether to participate, including risks to a spouse
1355 or partner associated with trials of, for example, psychotropic or genital-tract
1356 medicaments. (See also Guideline 8 Commentary, *Risks to groups of persons.*)

1357

1358 *Exception to the requirement of informed consent for interventional studies to include*
1359 *persons rendered incapable of informed consent by an acute condition.* Certain
1360 persons with acute conditions that render them incapable of giving informed consent

1361 may be eligible for inclusion in a study concerning an acute condition in which the
1362 majority of prospective subjects will be capable of informed consent, and in which the
1363 investigational intervention would hold out the prospect of direct benefit and would
1364 be justified accordingly. When the investigation involves certain procedures or
1365 interventions that would not be of direct benefit yet carry no more than minimal risk
1366 (such as the collection of additional blood for research purposes), the initial protocol
1367 submitted for approval to the ethical review committee should anticipate that some
1368 persons may be incapable of consent, and should propose for such patients a form of
1369 proxy consent, such as permission of the responsible relative. When the ethical review
1370 committee has approved or cleared such a protocol, an investigator may seek the
1371 permission of the responsible relative and enrol such a person.

1372

1373

Guideline 7

1374

Compensation for participation

1375

1376 **Subjects may be reimbursed for lost earnings, travel costs and other expenses**
1377 **incurred in taking part in a study; they may also receive free medical services.**

1378 **Subjects, particularly those who receive no direct benefit from research, may**
1379 **also be paid or otherwise compensated for inconvenience and time spent. The**

1380 **payments should not be so large, however, or the medical services so**
1381 **extensive as to induce prospective subjects to consent to participate in the**

1382 **research against their better judgment ("undue inducement"). All payments,**
1383 **reimbursements and medical services provided to research subjects must**

1384 **have been approved by an ethical review committee.**

1385

Commentary on Guideline 7

1387

1388 *Acceptable recompense.* Research subjects may be reimbursed for their transport and
1389 other expenses, including lost earnings, associated with their participation in research.

1390 Those who receive no direct benefit from the research may also receive a small sum

1391 of money for inconvenience due to their participation in the research. All subjects

1392 may receive medical services unrelated to the research and have procedures and tests

1393 performed free of charge.

1394

1395 *Unacceptable recompense.* Payments in money or in kind to research subjects should
1396 not be so large as to persuade them to take undue risks or volunteer against their better
1397 judgment. Payments or rewards that undermine a person's capacity to exercise free
1398 choice invalidate consent. It may be difficult to distinguish between suitable
1399 recompense and undue influence to participate in research. An unemployed person or
1400 a student may view promised recompense differently from an employed person.
1401 Someone without access to medical care may or may not be unduly influenced to
1402 participate in research simply to receive such care. A prospective subject may be
1403 induced to participate in order to obtain a better diagnosis or access to a drug not
1404 otherwise available; local ethical review committees may find such inducements
1405 acceptable. Monetary and in-kind recompense must, therefore, be evaluated in the
1406 light of the traditions of the particular culture and population in which they are
1407 offered, to determine whether they constitute undue influence. The ethical review
1408 committee will ordinarily be the best judge of what constitutes reasonable material
1409 recompense in particular circumstances. When research interventions or procedures
1410 that do not hold out the prospect of direct benefit present more than minimal risk, all
1411 parties involved in the research—sponsors, investigators and ethical review committees
1412—in both funding and host countries should be careful to avoid undue material
1413 inducement.

1414

1415 *Incompetent persons.* Incompetent persons may be vulnerable to exploitation for
1416 financial gain by guardians. A guardian asked to give permission on behalf of an
1417 incompetent person should be offered no recompense other than a refund of travel and
1418 related expenses.

1419

1420 *Withdrawal from a study.* A subject who withdraws from research for reasons related
1421 to the study, such as unacceptable side-effects of the intervention being studied, or
1422 who is withdrawn on health grounds, should be paid or recompensed as if full
1423 participation had taken place. A subject who withdraws for any other reason should be
1424 paid in proportion to the amount of participation. An investigator who must remove a
1425 subject from the study for wilful noncompliance is entitled to withhold part or all of
1426 the payment.

1427

1428

Guideline 8

1429

Benefits, harms and risks of study participation

1430

1431 **For all epidemiological research involving human subjects, the investigator**
1432 **must ensure that potential benefits and harms are reasonably balanced and**
1433 **risks are minimized.**

1434

1435 • **Interventions or procedures that hold out the prospect of direct**
1436 **diagnostic, therapeutic or preventive benefit for the individual subject must**
1437 **be justified by the expectation that they will be at least as advantageous to**
1438 **the individual subject, in the light of foreseeable harms and benefits, as any**
1439 **available alternative. Risks of such 'beneficial' interventions or procedures**
1440 **must be justified in relation to expected benefits to the individual subject.**

1441

1442 • **Risks of interventions that do not hold out the prospect of direct**
1443 **diagnostic, therapeutic or preventive benefit for the individual must be**
1444 **justified in relation to the expected benefits to society. The risks presented**
1445 **by such interventions must be reasonable in relation to the importance of**
1446 **the knowledge to be gained.**

1447

Commentary on Guideline 8

1449

1450 *Ethical grounding.* The Declaration of Helsinki in several paragraphs deals with the
1451 well-being of research subjects and the avoidance of harm, specifically:
1452 considerations related to the well-being of the human subject should take precedence
1453 over the interests of science and society (*Paragraph 5*); clinical testing must be
1454 preceded by adequate laboratory or animal experimentation to demonstrate a
1455 reasonable probability of success without undue risk (*Paragraph 11*); every project
1456 should be preceded by careful assessment of predictable harms and burdens in
1457 comparison with foreseeable benefits to the subject or to others (*Paragraph 16*);
1458 physician-researchers must be confident that the risks involved have been adequately
1459 assessed and can be satisfactorily managed (*Paragraph 17*); and the harms and
1460 burdens to the subject must be minimized, and reasonable in relation to the

1461 importance of the objective or the knowledge to be gained (*Paragraph 18*).

1462 Epidemiological studies may employ a variety of interventions of which some
1463 hold out the prospect of direct therapeutic benefit (beneficial interventions) and others
1464 are administered solely to answer the research question (non-beneficial interventions).
1465 Beneficial interventions are justified as they are in medical practice by the expectation
1466 that they will be at least as advantageous to the individuals concerned, in the light of
1467 both harms and benefits, as any available alternative. Non-beneficial interventions are
1468 assessed differently; they may be justified only by appeal to the knowledge to be
1469 gained, either “generalizable knowledge” (the usual objective of a research project) or
1470 more particularized findings, of use for example by public health officials.

1471 Paragraphs 5 and 18 of the Declaration of Helsinki do not preclude well-
1472 informed volunteers, capable of fully appreciating risks and benefits of an
1473 investigation, from participating in research for altruistic reasons or for modest
1474 remuneration.

1475

1476 *Experimental studies of preventive interventions.* Epidemiologists carry out
1477 experimental studies, in particular randomized population trials, usually to test
1478 preventive intervention programmes, for instance administration of a vaccine or a
1479 drug, or an organized screening programme. Because they involve the totality of a
1480 population or a relevant segment of it (e.g., those believed to be at higher risk of the
1481 target disease), these interventions imply that everybody will be submitted to
1482 whatever inconvenience and potential harm the intervention entails, while only the
1483 minority (often, comparatively small), namely those who would have actually
1484 developed the disease, get the benefit of avoiding it thanks to the intervention (the
1485 same applies, although to a lesser degree, even when the intervention is concentrated
1486 on so-called "high risk" groups). This is an inherent problem of preventive
1487 programmes; both investigators and ethical review committees need to carefully
1488 weigh the potential harm and inconvenience to programme participants who may not
1489 receive any benefit from the programme, and the participants must receive clear and
1490 full information before giving their consent. Likewise, research may be conducted on
1491 a screening programme for a condition for which no effective treatment exists
1492 provided the results could be of sufficient direct relevance to the health of people

1493 other than the participants in the study (for example, in developing a programme for a
1494 transmissible disease, whether contagious or genetic).

1495

1496 *Minimizing risk associated with participation in a randomized study.* In a randomized
1497 controlled study subjects risk being allocated to receive the intervention that proves
1498 inferior. They are allocated by chance to one of two or more intervention arms and
1499 followed to a predetermined end-point. (Interventions are understood to include new
1500 or established therapies, diagnostic tests and preventive measures.) An intervention is
1501 evaluated by comparing it with another intervention (a control), which is ordinarily
1502 the best current method, selected from the safe and effective treatments available
1503 globally, unless some other control intervention such as placebo can be justified
1504 ethically (see Guideline 11).

1505 To minimize risk when the intervention to be tested is designed to prevent or
1506 postpone a lethal or disabling outcome, the investigator must not, for experimental
1507 purposes, withhold therapy that is known to be superior to the intervention being
1508 tested, unless the withholding can be justified by the standards set forth in Guideline
1509 11. Also, the investigator must provide in the research protocol for the monitoring of
1510 research data by an independent board (Data and Safety Monitoring Board); one
1511 function of such a board is to protect the research subjects from previously unknown
1512 adverse reactions or unnecessarily prolonged exposure to an inferior therapy.
1513 Normally at the outset of a randomized controlled study, criteria are established for its
1514 premature termination (stopping rules or guidelines).

1515

1516 *Risks to groups of persons.* In order to achieve the social benefits anticipated from
1517 conducting research, results should be made public. Sometimes, however, research in
1518 epidemiology (as well as such other fields as genetics and sociology) may present
1519 risks to the interests of communities, societies, or racially or ethnically defined
1520 groups. Information might be published that could stigmatize a group or expose its
1521 members to discrimination. Such information, for example, could indicate that the
1522 group has a higher than average prevalence of alcoholism, mental illness or sexually
1523 transmitted disease, or is particularly susceptible to certain genetic disorders. Plans to
1524 conduct such research should be sensitive to such considerations, to the need to
1525 maintain confidentiality during and after the study, and to the need to publish the

1526 resulting data in a manner that is respectful of the interests of all concerned, or in
1527 certain exceptional circumstances not to publish them. The ethical review committee
1528 should ensure that the interests of all concerned are given due consideration; often it
1529 will be advisable to have individual consent supplemented by community
1530 consultation. In assessing the harms and benefits that a protocol presents to a
1531 population, it is appropriate to consider the harm that could result from forgoing the
1532 research or from failing to publish the results.

1533

1534 [The ethical basis for the justification of risk is elaborated further in
1535 Guideline 9]

1536

1537

Guideline 9

1538 ***Special limitations on risk when research involves individuals***
1539 ***who are not capable of giving informed consent***

1540

1541 **When there is ethical and scientific justification to conduct research with**
1542 **individuals incapable of giving informed consent, the potential harm from any**
1543 **research intervention that does not hold out the prospect of direct benefit for**
1544 **the individual subject should not be more than minimal.**

1545

1546 ***Commentary on Guideline 9***

1547

1548 *The minimal-risk standard.* Certain individuals or groups may have limited or no
1549 capacity to give informed consent either because, as in the case of prisoners, their
1550 autonomy is limited, or because they have limited cognitive capacity. Research
1551 involving such persons that does not aim to benefit them directly may occur only
1552 when its potential risks are found to be no more than minimal.

1553 In addition, the ethical review committee must find: 1) that the research is
1554 designed to be responsive to the disease or condition affecting the prospective
1555 subjects or to conditions to which they are particularly susceptible; 2) that the
1556 objective of the research is sufficiently important to justify exposure of the subjects to
1557 the increased risk; and 3) that the interventions are reasonably comparable to the
1558 clinical interventions that the subjects have experienced or may be expected to

1559 experience in relation to the condition under investigation. The requirement that the
1560 research interventions be reasonably comparable is intended to enable the subjects to
1561 draw on personal experience as they decide whether to accept or reject additional
1562 procedures for research purposes. Their choices will, therefore, be more informed
1563 even though they may not fully meet the standard of informed consent.

1564

1565 *Consent required when subject becomes capable of informed consent.* If such research
1566 subjects, including children, become capable of giving independent informed consent
1567 during the research, their consent to continued participation should be obtained.

1568

1569 (See also Guidelines 4, 13, 14 and 15.)

1570

1571

Guideline 10

1572

Research in populations and communities

1573

with limited resources

1574

1575 **Before undertaking research in a population or community with limited**
1576 **resources, the sponsor and the investigator must make every effort to ensure**
1577 **that:**

1578

1579 - **the research is responsive to the health needs and the priorities of the**
1580 **population or community in which it is to be carried out; and**

1581

1582 - **any intervention or product developed, or knowledge generated, will be**
1583 **made reasonably available for the benefit of that population or community.**

1584

Commentary on Guideline 10

1586

1587 This Guideline is concerned with countries or communities in which resources
1588 are limited to the extent that the population is, or may be, vulnerable to exploitation
1589 by sponsors and investigators from the relatively wealthy countries and communities.
1590 This concern, which has arisen principally from experiences with clinical trials of new
1591 drugs, should not stand in the way of carrying out ethically sound epidemiological

1592 studies in resource-limited setting. Such studies are, almost by nature, relevant to the
1593 health of the populations or communities in which they are conducted, and the
1594 information gathered in such studies can often be very important for improving
1595 population health in resource-poor countries and communities.

1596

1597 *Responsiveness of research to health needs and priorities.* To meet the ethical
1598 requirement that research be responsive to the health needs of the population or
1599 community in which it is carried, it is not sufficient simply to determine that a disease
1600 is prevalent in the population and that new or further research is needed: the ethical
1601 requirement of “responsiveness” can be fulfilled only if successful interventions or
1602 other kinds of health benefit are made available to the population. This is applicable
1603 especially to research conducted in countries where governments lack the resources to
1604 make such products or benefits widely available. Even when a product to be tested in
1605 a particular country is much cheaper than the standard treatment in some other
1606 countries, the government or individuals in that country may still be unable to afford
1607 it. If the knowledge gained from the research in such a country is used primarily for
1608 the benefit of populations that can afford the tested product, the research may rightly
1609 be characterized as exploitative and, therefore, unethical.

1610 When an investigational intervention has important potential for health care in
1611 the host country, the negotiation that the sponsor should undertake to determine the
1612 practical implications of "responsiveness", as well as "reasonable availability", should
1613 include representatives of stakeholders in the host country; these include the national
1614 government, the health ministry, local health authorities, and concerned scientific and
1615 ethics groups, as well as representatives of the communities from which subjects are
1616 drawn and non-governmental organizations such as health advocacy groups. The
1617 negotiation should cover the health-care infrastructure required for safe and rational
1618 use of the intervention, the likelihood of authorization for distribution, and decisions
1619 regarding payments, royalties, subsidies, technology and intellectual property, as well
1620 as distribution costs, when this economic information is not proprietary. In some
1621 cases, satisfactory discussion of the availability and distribution of successful
1622 products will necessarily engage international organizations, donor governments and
1623 bilateral agencies, international nongovernmental organizations, and the private
1624 sector. The development of a health-care infrastructure should be facilitated at the

1625 onset so that it can be of use during and beyond the conduct of the research.

1626 Additionally, if an investigational intervention has been shown to be beneficial,
1627 the sponsor should continue to provide it to the subjects after the conclusion of the
1628 study and pending its approval by a drug regulatory authority, when relevant. The
1629 sponsor is unlikely to be in a position to make a beneficial investigational intervention
1630 generally available to the community or population until some time after the
1631 conclusion of the study, as it may be in short supply and in any case cannot be made
1632 generally available before a drug regulatory authority has approved it.

1633 When a study's expected outcome is scientific knowledge rather than a
1634 commercial product, such planning or negotiation is rarely, if ever, needed. There
1635 must be assurance, however, that the scientific knowledge developed will be used for
1636 the benefit of the population.

1637

1638 *Reasonable availability.* The issue of "reasonable availability" is complex and will
1639 need to be determined on a case-by-case basis. Relevant considerations include the
1640 length of time for which the intervention or product developed, or other agreed
1641 benefit, will be made available to research subjects, or to the community or
1642 population concerned; the severity of a subject's medical condition; the effect of
1643 withdrawing the study drug (e.g., death of a subject); the cost to the subject or health
1644 service; and the question of undue inducement if an intervention is provided free of
1645 charge.

1646 In general, if there is good reason to believe that a product developed or
1647 knowledge generated by research is unlikely to be reasonably available to, or applied
1648 to the benefit of, the population of a proposed host country or community after the
1649 conclusion of the research, it is unethical to conduct the research in that country or
1650 community. This should not be construed as precluding studies designed to evaluate
1651 novel therapeutic concepts. As a rare exception, for example, research may be
1652 designed to obtain preliminary evidence that a drug or a class of drugs has a beneficial
1653 effect in the treatment of a disease that occurs only in regions with extremely limited
1654 resources, and it could not be carried out reasonably well in more developed
1655 communities. Such research may be justified ethically even if there is no plan in place
1656 to make a product available to the population of the host country or community at the
1657 conclusion of the preliminary phase of its development. If the concept is found to be

1658 valid, subsequent phases of the research could result in a product that could be made
1659 reasonably available at its conclusion.

1660

1661 (See also Guidelines 3,12, 20 and 21.)

1662

1663 ***Guideline 11***

1664 ***Choice of control in clinical trials***

1665

1666 **As a general rule, research subjects in the control group of a trial of a**
1667 **diagnostic, therapeutic, or preventive intervention should receive an**
1668 **established effective intervention. In some circumstances it may be ethically**
1669 **acceptable to use an alternative comparator, such as placebo or "no**
1670 **treatment".**

1671

1672 **Placebos may be used:**

1673

1674 - **when there is no established effective intervention;**

1675

1676 - **when withholding an established effective intervention would expose**
1677 **subjects to, at most, temporary discomfort or delay in relief of symptoms;**

1678

1679 - **when use of an established effective intervention as comparator would**
1680 **not yield scientifically reliable results and use of placebo would not add**
1681 **any risk of serious or irreversible harm to the subjects.**

1682

1683 ***Commentary on Guideline 11***

1684

1685 The controversies that have arisen concerning placebo controls have centred
1686 largely on clinical trials of new drugs undertaken in resource-poor countries by
1687 investigators from resource-rich countries. Nonetheless, ethical issues can also arise
1688 when placebos are proposed as part of the design of interventional studies undertaken
1689 by epidemiologists.

1690

1691 *General considerations for controlled clinical trials.* The design of trials of

1692 investigational diagnostic, therapeutic or preventive interventions raises interrelated
1693 scientific and ethical issues for sponsors, investigators and ethical review committees.
1694 To obtain reliable results, investigators must compare the effects of an investigational
1695 intervention on subjects assigned to the investigational arm (or arms) of a trial with
1696 the effects that a control intervention produces in subjects drawn from the same
1697 population and assigned to its control arm. Although randomization is the preferred
1698 method for assigning subjects to the various arms of a clinical trial, non-experimental
1699 methods, such as cohort and case-control studies to evaluate drugs and devices, may
1700 often be justified scientifically and ethically. Assignment to treatment arms by
1701 randomization, in addition to its usual scientific superiority, offers the advantage of
1702 tending to render equivalent to all subjects the foreseeable benefits and risks of
1703 participation in a trial.

1704 A clinical trial cannot be justified ethically unless it is capable of producing
1705 scientifically reliable results. When the objective is to establish the effectiveness and
1706 safety of an investigational intervention, the use of a placebo control is sometimes
1707 much more likely than the use of an active control to produce a scientifically reliable
1708 result. In many cases the ability of a trial to distinguish effective from ineffective
1709 interventions (its assay sensitivity) cannot be assured unless the control is a placebo.
1710 If, however, an effect of using a placebo would be to deprive subjects in the control
1711 arm of an established effective intervention, and thereby to expose them to serious
1712 harm, particularly if it is irreversible, it would obviously be unethical to use a placebo.

1713

1714 *Placebo control in the absence of a established effective alternative.* The use of
1715 placebo in the control arm of a clinical trial is ethically acceptable when, as stated in
1716 the Declaration of Helsinki (Paragraph 29), “no proven prophylactic, diagnostic or
1717 therapeutic method exists.” Usually, in this case, a placebo is scientifically preferable
1718 to no intervention. In certain circumstances, however, an alternative design may be
1719 both scientifically and ethically acceptable, and preferable; for example, in certain
1720 vaccine trials an investigator might choose to provide for those in the control arm a
1721 vaccine that is unrelated to the investigational vaccine.

1722

1723 *Placebo-controlled studies that entail only minor risks.* A placebo-controlled design
1724 may be ethically acceptable, and preferable on scientific grounds, when the condition

1725 for which the intervention is being evaluated is only a small deviation in physiological
1726 measurements, such as slightly raised blood pressure or a modest increase in serum
1727 cholesterol, and if delaying or omitting an established effective intervention would
1728 cause only temporary discomfort (e.g., common headache) and no serious adverse
1729 consequences. Likewise, when the investigative intervention is aimed at a relatively
1730 trivial condition, such as the common cold or hair loss, and using a placebo for the
1731 duration of a trial would deprive control subjects of only minor benefits, it is not
1732 unethical to use a placebo-control design. Even if it were possible to design a so-
1733 called “non-inferiority”, or “equivalency”, trial using an active control, it would still
1734 not be unethical in these circumstances to use a placebo-control design. The ethical
1735 acceptability of such placebo-controlled studies increases as the period of placebo use
1736 is decreased, and when the study design permits change to the active intervention
1737 (“escape treatment”) if intolerable symptoms occur. In any event, the ethical review
1738 committee must be fully satisfied that the risks of withholding such an intervention
1739 are truly minor and short-lived, that the safety and human rights of the subjects will be
1740 fully protected, that prospective subjects will be fully informed about alternative
1741 treatments, and that the purpose and design of the study are scientifically sound.

1742

1743 *Placebo control when active control would not yield reliable results.* Another
1744 rationale for using a placebo control rather than an established effective intervention
1745 is that the documented experience with the established effective intervention is not
1746 sufficient to provide a scientifically reliable comparison with the intervention being
1747 investigated; it is then difficult, or even impossible, without using a placebo, to design
1748 a scientifically reliable study. (When a researcher relies on this rationale, the ethical
1749 review committee has the option of seeking expert opinion as to whether use of an
1750 established effective intervention in the control arm would invalidate the results of the
1751 research.) This basis for depriving control subjects of an established effective
1752 intervention in clinical trials is, however, ethically acceptable only when doing so
1753 would not add any risk of serious, particularly irreversible, harm to the subjects. In
1754 some cases, the condition at which the intervention is aimed (for example, cancer or
1755 HIV/AIDS) will be too serious to deprive control subjects of an established effective
1756 intervention.

1757

1758 An exception to this general rule is applicable in some studies designed to
1759 develop a therapeutic, preventive or diagnostic intervention for use in a country or
1760 community in which established effective interventions used in other countries are not
1761 available, and are unlikely to become available in the foreseeable future, for economic
1762 or logistic reasons, when the purpose of such a study is to make a potentially effective
1763 and affordable alternative available to the population. An example might be an
1764 interventional epidemiological study of a simple method of water purification that
1765 could eliminate most pathogens responsible for serious disease in a country that is
1766 unable to afford more elaborate interventions which are effective in countries with
1767 greater resources. The scientific and ethical review committees must be satisfied that
1768 the established effective intervention cannot be used as comparator because its use
1769 would not yield scientifically reliable results that would be relevant to the health
1770 needs of the study population. This would be the case when existing data about the
1771 effectiveness and safety of the established effective intervention may have been
1772 accumulated under circumstances unlike those of the population in which it is
1773 proposed to conduct the trial (e.g., the disease or condition manifests itself differently
1774 in different populations, or other uncontrolled factors exist in the environment). In
1775 these circumstances an ethical review committee may approve a clinical trial in which
1776 the comparator is a placebo or no treatment or a local remedy. The ethical
1777 acceptability of such a proposed investigational intervention depends upon its being
1778 responsive to the health needs of the population from which the research subjects
1779 would be recruited and upon there being assurance that, if it proves to be safe and
1780 effective, it will be made reasonably available to that population.

1781

1782 *An "equivalency trial" as an alternative to a placebo-controlled trial.* An
1783 alternative to a placebo-control design would be an "equivalency trial", which would
1784 compare an investigational intervention with an established effective intervention.
1785 Equivalency trials are not designed to determine whether an investigational
1786 intervention is superior to an established effective one but rather whether it is, in
1787 effectiveness and safety, equivalent, or almost equivalent, to the latter; it would be
1788 hazardous to conclude, however, that an intervention that meets this equivalency
1789 standard is better than nothing or whatever intervention is available in the country
1790 simply because the intervention used as the control was itself previously shown to be

1791 better than a placebo, since there may be substantial differences between the results of
1792 superficially identical clinical trials carried out in different countries or at different
1793 times.

1794

1795 *Means of minimizing harm to placebo-control subjects.* Even when placebo
1796 controls are justified on one of the bases set forth in the Guideline, there are means of
1797 minimizing the possibly harmful effect of being in the control arm.

1798 First, a placebo-control group need not be untreated. An add-on design may be
1799 employed when the investigational therapy and a standard treatment have different
1800 mechanisms of action. The treatment to be tested and placebo are each added to a
1801 standard treatment. Such studies have a particular place when a standard treatment is
1802 known to decrease mortality or irreversible morbidity but a trial with standard
1803 treatment as the active control cannot be carried out or would be difficult to interpret
1804 [*International Conference on Harmonisation (ICH) Guideline: Choice of Control*
1805 *Group and Related Issues in Clinical Trials, 2000*]. In testing for improved treatment
1806 of life-threatening diseases such as cancer, HIV/AIDS, or heart failure, add-on
1807 designs are a particularly useful means of finding improvements in interventions that
1808 are not fully effective or may cause intolerable side-effects. They have a place also in
1809 respect of treatment for epilepsy, rheumatism and osteoporosis, for example, because
1810 withholding of established effective therapy could result in progressive disability,
1811 unacceptable discomfort or both.

1812 Second, as indicated in Guideline 8 Commentary, when the intervention to be
1813 tested in a randomized controlled trial is designed to prevent or postpone a lethal or
1814 disabling outcome, the investigator minimizes harmful effects of placebo-control
1815 studies by providing in the research protocol for the monitoring of research data by an
1816 independent Data and Safety Monitoring Board (DSMB). One function of such a
1817 board is to protect the research subjects from previously unknown adverse reactions;
1818 another is to avoid unnecessarily prolonged exposure to an inferior intervention. The
1819 board fulfils the latter function by means of interim analyses of the data pertaining to
1820 efficacy to ensure that the trial does not continue beyond the point at which an
1821 investigational therapy is demonstrated to be effective. Normally, at the outset of a
1822 randomized controlled trial, criteria are established for its premature termination
1823 (stopping rules or guidelines).

1824 In some cases the DSMB is called upon to perform "conditional power
1825 calculations", designed to determine the probability that a particular clinical trial
1826 could ever show that the investigational therapy is effective. If that probability is very
1827 small, the DSMB is expected to recommend termination of the clinical trial, because
1828 it would be unethical to continue it beyond that point.

1829 In most cases of research involving human subjects, it is unnecessary to appoint
1830 a DSMB. To ensure that research is carefully monitored for the early detection of
1831 adverse events, the sponsor or the principal investigator appoints an individual to be
1832 responsible for advising on the need to consider changing the system of monitoring
1833 for adverse events or the process of informed consent, or even to consider terminating
1834 the study.

1835

1836

Guideline 12

1837

Equitable distribution of burdens and benefits in the selection of groups of subjects in research

1838

1839

1840 **Groups or communities to be invited to be subjects of research should be**
1841 **selected in such a way that the burdens and benefits of the research will be**
1842 **equitably distributed. The exclusion of groups or communities that might**
1843 **benefit from study participation must be justified.**

1844

Commentary on Guideline 12

1846

1847 *General considerations:* Equity requires that no group or class of persons should
1848 bear more than its fair share of the burdens of participation in research. Similarly, no
1849 group should be deprived of its fair share of the benefits of research, short-term or
1850 long-term; such benefits include the direct benefits of participation as well as the
1851 benefits of the new knowledge that the research is designed to yield. When burdens or
1852 benefits of research are to be apportioned unequally among individuals or groups of
1853 persons, the criteria for unequal distribution should be morally justifiable and not
1854 arbitrary. In other words, unequal allocation must not be inequitable. Subjects should
1855 be drawn from the qualifying population in the general geographic area of the trial
1856 without regard to race, ethnicity, economic status or gender unless there is a sound

1857 scientific reason to do otherwise.

1858 In the past, groups of persons were excluded from participation in research for
1859 what were then considered good reasons. As a consequence of such exclusions,
1860 information about the diagnosis, prevention and treatment of diseases in such groups
1861 of persons is limited. This has resulted in a serious class injustice. If information
1862 about the management of diseases is considered a benefit that is distributed within a
1863 society, it is unjust to deprive groups of persons of that benefit. Such documents as
1864 the Declaration of Helsinki and the UNAIDS Guidance Document *Ethical*
1865 *Considerations in HIV Preventive Vaccine Research*, and the policies of many
1866 national governments and professional societies, recognize the need to redress these
1867 injustices by encouraging the participation of previously excluded groups in basic and
1868 applied biomedical research. [NOTE: *Have epidemiologists' groups done likewise?*]

1869 Members of vulnerable groups also have the same entitlement to access to the
1870 benefits of investigational interventions that show promise of therapeutic benefit as
1871 persons not considered vulnerable, particularly when no superior or equivalent
1872 approaches to therapy are available.

1873 There has been a perception, sometimes correct and sometimes incorrect, that
1874 certain groups of persons have been overused as research subjects. In some cases such
1875 overuse has been based on the administrative availability of the populations. Research
1876 hospitals are often located in places where members of the lowest socioeconomic
1877 classes reside, and this has resulted in an apparent overuse of such persons. Other
1878 groups that may have been overused because they were conveniently available to
1879 researchers include students in investigators' classes, residents of long-term care
1880 facilities and subordinate members of hierarchical institutions. Impoverished groups
1881 have been overused because of their willingness to serve as subjects in exchange for
1882 relatively small stipends. Prisoners have been considered ideal subjects for Phase I
1883 drug studies because of their highly regimented lives and, in many cases, their
1884 conditions of economic deprivation.

1885 Overuse of certain groups, such as the poor or the administratively available, is
1886 unjust for several reasons. It is unjust to selectively recruit impoverished people to
1887 serve as research subjects simply because they can be more easily induced to
1888 participate in exchange for small payments. A further injustice occurs when such
1889 people are called upon to bear the burdens of research while others who are better off

1890 enjoy the benefits. However, although the burdens of research should not fall
1891 disproportionately on socio-economically disadvantaged groups, neither should such
1892 groups be categorically excluded from research protocols. It would not be unjust to
1893 selectively recruit poor people to serve as subjects in research designed to address
1894 problems that are prevalent in their group – malnutrition or poor living conditions, for
1895 example. Similar considerations apply to institutionalized groups or those whose
1896 availability to the investigators is for other reasons administratively convenient.

1897 Not only may certain groups within a society be inappropriately overused as
1898 research subjects, but also entire communities or societies may be overused. This has
1899 been particularly likely to occur in countries or communities with insufficiently well-
1900 developed systems for the protection of the rights and welfare of human research
1901 subjects. Such overuse is especially questionable when the populations or
1902 communities concerned bear the burdens of participation in research but are
1903 extremely unlikely ever to enjoy the benefits of new knowledge and products
1904 developed as a result of the research. (See Guideline 10: *Research in populations and*
1905 *communities with limited resources.*)

1906

1907

Guideline 13

1908

Research involving vulnerable persons

1909

1910 **Special justification is required for inviting vulnerable individuals to serve as**
1911 **research subjects and, if they are selected, the means of protecting their rights**
1912 **and welfare must be strictly applied.**

1913

Commentary on Guideline 13

1915

1916 Vulnerable persons are those who are relatively (or absolutely) incapable of
1917 protecting their own interests. More formally, they may have insufficient power,
1918 intelligence, education, resources, strength, or other needed attributes to protect their
1919 own interests.

1920

1921 *General considerations.* The central problem presented by plans to involve vulnerable
1922 persons as research subjects is that such plans may entail an inequitable distribution of

1923 the burdens and benefits of research participation. Ethical justification of their
1924 involvement usually requires that investigators satisfy ethical review committees that:

1925

- 1926 – the research could not be carried out equally well with less vulnerable
1927 subjects;
- 1928 – the research is intended to obtain knowledge that will lead to improved
1929 diagnosis, prevention or treatment of diseases or other health problems
1930 characteristic of, or unique to, the vulnerable class– either the actual subjects
1931 or other similarly situated members of the vulnerable class;
- 1932 – research subjects and other members of the vulnerable class from which
1933 subjects are recruited will ordinarily be assured reasonable access to any
1934 diagnostic, preventive or therapeutic products that will become available as a
1935 consequence of the research;
- 1936 – the risks attached to interventions or procedures that do not hold out the
1937 prospect of direct health-related benefit will not exceed those associated with
1938 routine medical or psychological examination of such persons unless an
1939 ethical review committee authorizes a slight increase over this level of risk
1940 (Guideline 9); and,
- 1941 – when the prospective subjects are either incompetent or otherwise
1942 substantially unable to give informed consent, their agreement will be
1943 supplemented by the permission of their legal guardians or other appropriate
1944 representatives (Guidelines 14 and 15).

1945

1946 *Vulnerable groups.* Major classes of individuals conventionally considered vulnerable
1947 are those with limited capacity or freedom either to consent or to decline to consent.
1948 They include children, and persons who because of mental or behavioural disorders
1949 are incapable of giving informed consent. Less obvious as a vulnerable group are
1950 prospective subjects who are junior or subsidiary members of a hierarchical group; the
1951 quality of their consent requires careful consideration, since their agreement to
1952 volunteer may be unduly influenced, whether justified or not, by the expectation of
1953 preferential treatment if they agree or by fear of disapproval or retaliation if they
1954 refuse. Examples of such groups are medical and nursing students, subordinate
1955 hospital and laboratory personnel, employees of pharmaceutical companies, and

1956 members of the armed forces or police. Because they work in close proximity to
1957 investigators, they tend to be called upon more often than others to serve as research
1958 subjects, and this could result in inequitable distribution of the burdens and benefits of
1959 research.

1960 Elderly persons are commonly regarded as vulnerable. With advancing age,
1961 people are increasingly likely to acquire attributes that define them as vulnerable.
1962 They may, for example, be institutionalized or develop varying degrees of dementia.
1963 If and when they acquire such vulnerability-defining attributes, and not before, it is
1964 appropriate to consider them vulnerable and to treat them accordingly.

1965 Other groups or classes may also be considered vulnerable. They include
1966 residents of nursing homes, people receiving welfare benefits or social assistance and
1967 other poor people and the unemployed, patients in emergency rooms, some ethnic and
1968 racial minority groups, homeless persons, nomads, refugees or displaced persons,
1969 prisoners, patients with incurable disease, individuals who are politically powerless,
1970 and members of communities unfamiliar with modern medical concepts. To the extent
1971 that these and other classes of people have attributes resembling those of classes
1972 identified as vulnerable, the need for special protection of their rights and welfare
1973 should be reviewed and applied, where relevant.

1974 Although, on the whole, investigators must study less vulnerable groups before
1975 involving more vulnerable groups, some exceptions are justified. In general, children
1976 are not suitable for Phase I drug trials or for Phase I or II vaccine trials, but such trials
1977 may be permissible after studies in adults have shown some therapeutic or preventive
1978 effect. For example, a Phase II vaccine trial seeking evidence of immunogenicity in
1979 infants may be justified when a vaccine has shown evidence of preventing or slowing
1980 progression of an infectious disease in adults, or Phase I research with children may
1981 be appropriate because the disease to be treated does not occur in adults or is
1982 manifested differently in children.

1983

1984

Guideline 14

1985

Research involving children

1986

1987 **Before undertaking research involving children, the investigator must ensure**

1988 **that:**

- 1989 – **the research might not equally well be carried out with adults;**
- 1990 – **the purpose of the research is to obtain knowledge relevant to the health**
- 1991 **needs of children;**
- 1992 – **a parent or legal representative of each child has given permission;**
- 1993 – **the agreement (assent) of each child has been obtained to the extent of**
- 1994 **the child's capabilities; and**
- 1995 – **a child's refusal to participate or continue in the research will be**
- 1996 **respected.**

1997

Commentary on Guideline 14

1999

2000 *Justifications for involving children in interventional studies.* The participation of
2001 children is indispensable for research into diseases of childhood and conditions to
2002 which children are particularly susceptible (*cf.* vaccine trials), as well as for clinical
2003 trials of drugs that are designed for children as well as adults. In the past, many new
2004 products were not tested for children though they were directed towards diseases also
2005 occurring in childhood; thus children either did not benefit from these new drugs or
2006 were exposed to them though little was known about their specific effects or safety in
2007 children. Now it is widely agreed that, as a general rule, the sponsor of any new
2008 therapeutic, diagnostic or preventive product that is likely to be indicated for use in
2009 children is obliged to evaluate its safety and efficacy for children before it is released
2010 for general distribution.

2011

2012 *Justifications for involving children in other epidemiological studies.* Observational
2013 epidemiological research, such as studies on how genetic and environmental factors
2014 present in childhood affect adult health, may be carried out even when the purpose is
2015 not "to obtain knowledge relevant to the health needs of children" provided that the
2016 other requirements are met. Since the potential benefits (in terms of etiological

2017 knowledge derived from the study) are relevant to adults while the potential harm
2018 would affect the children, such studies are usually permissible only in the context of
2019 the extremely reduced risks found in observational research. A further justification
2020 would arise when the children in the study would also be potential beneficiaries of the
2021 study results when they become adults.

2022 Research on occupational hazards for children at work, which would produce
2023 knowledge relevant to children's health but may not meet the other requirements (e.g.,
2024 if it might instead be carried out with adults), should nonetheless be regarded as
2025 permissible and even necessary, if nothing else to document the persistence and extent
2026 of child labor practices.

2027

2028 *Assent of the child in studies for which competent subjects' consent is required.* The
2029 willing cooperation of the child should be sought, after the child has been informed to
2030 the extent that the child's maturity and intelligence permit. The age at which a child
2031 becomes legally competent to give consent differs substantially from one jurisdiction
2032 to another; in some countries the "age of consent" established in their different
2033 provinces, states or other political subdivisions varies considerably. Often children
2034 who have not yet reached the legally established age of consent can understand the
2035 implications of informed consent and go through the necessary procedures; they can
2036 therefore knowingly agree to serve as research subjects. Such knowing agreement,
2037 sometimes referred to as assent, is insufficient to permit participation in research
2038 unless it is supplemented by the permission of a parent, a legal guardian or other duly
2039 authorized representative.

2040 Some children who are too immature to be able to give knowing agreement, or
2041 assent, may be able to register a 'deliberate objection', an expression of disapproval or
2042 refusal of a proposed procedure. The deliberate objection of an older child, for
2043 example, is to be distinguished from the behaviour of an infant, who is likely to cry or
2044 withdraw in response to almost any stimulus. Older children, who are more capable of
2045 giving assent, should be selected before younger children or infants, unless there are
2046 valid scientific reasons for involving younger children first.

2047 A deliberate objection by a child to taking part in research should always be
2048 respected even if the parents have given permission, unless the child needs an
2049 intervention that is not available outside the context of research, the investigational

2050 intervention shows promise of therapeutic benefit, and there is no acceptable
2051 alternative therapy. In such a case, particularly if the child is very young or immature,
2052 a parent or guardian may override the child's objections. If the child is older and more
2053 nearly capable of independent informed consent, the investigator should seek the
2054 specific approval or clearance of the scientific and ethical review committees for
2055 initiating or continuing with the investigational treatment. If child subjects become
2056 capable of independent informed consent during the research, their informed consent
2057 to continued participation should be sought and their decision respected.

2058 A child with a likely fatal illness may object or refuse assent to continuation of
2059 a burdensome or distressing intervention. In such circumstances parents may press an
2060 investigator to persist with an investigational intervention against the child's wishes.
2061 The investigator may agree to do so if the intervention shows promise of preserving or
2062 prolonging life and there is no acceptable alternative treatment. In such cases, the
2063 investigator should seek the specific approval or clearance of the ethical review
2064 committee before agreeing to override the wishes of the child.

2065

2066 *Permission of a parent or guardian.* The investigator must obtain the permission of a
2067 parent or guardian in accordance with local laws or established procedures in all
2068 studies for which individual consent would be required from subjects capable of
2069 giving consent (see Guideline 4). It may be assumed that children over the age of 12
2070 or 13 years are usually capable of understanding what is necessary to give adequately
2071 informed consent, but their consent (assent) should normally be complemented by the
2072 permission of a parent or guardian, even when local law does not require such
2073 permission. Even when the law requires parental permission, however, the assent of
2074 the child must be obtained.

2075 In some jurisdictions, some individuals who are below the general age of
2076 consent are regarded as “emancipated” or “mature” minors and are authorized to
2077 consent without the agreement or even the awareness of their parents or guardians.
2078 They may be married or pregnant or be already parents or living independently. Some
2079 studies involve investigation of adolescents’ beliefs and behaviour regarding sexuality
2080 or use of recreational drugs; other research addresses domestic violence or child
2081 abuse. For studies on these topics, ethical review committees may waive parental
2082 permission if, for example, parental knowledge of the subject matter may place the

2083 adolescents at some risk of questioning or even intimidation by their parents.
2084 Because of the issues inherent in obtaining assent from children in institutions,
2085 such children should only exceptionally be subjects of research. In the case of
2086 institutionalized children without parents, or whose parents are not legally authorized
2087 to grant permission, the ethical review committee may require sponsors or
2088 investigators to provide it with the opinion of an independent, concerned, expert
2089 advocate for institutionalized children as to the propriety of undertaking the research
2090 with such children.

2091

2092 *Observation of research by a parent or guardian.* A parent or guardian who gives
2093 permission for a child to participate in research should be given the opportunity, to a
2094 reasonable extent, to observe the research as it proceeds, so as to be able to withdraw
2095 the child if the parent or guardian decides it is in the child's best interests to do so.

2096

2097 *Psychological and medical support.* Research involving children should be conducted
2098 in settings in which the child and the parent can obtain adequate medical and
2099 psychological support. As an additional protection for children, an investigator may,
2100 when possible, obtain the advice of a child's family physician, paediatrician or other
2101 health-care provider on matters concerning the child's participation in the research.

2102

2103 (See also Guidelines 8, 9 and 13.)

2104

2105

Guideline 15

2106 ***Research involving individuals who by reason of mental or***
2107 ***behavioural disorders are not capable of giving***
2108 ***adequately informed consent***

2109

2110 **Before undertaking research involving individuals who by reason of mental or**
2111 **behavioural disorders are not capable of giving adequately informed consent,**
2112 **the investigator must ensure that:**

2113

2114 – **such persons will not be subjects of research that might equally well**
2115 **be carried out on persons whose capacity to give adequately**

- 2116 **informed consent is not impaired;**
2117 – **the purpose of the research is to obtain knowledge relevant to the**
2118 **particular health needs of persons with mental or behavioural**
2119 **disorders;**
2120 – **the consent of each subject has been obtained to the extent of that**
2121 **person's capabilities, and a prospective subject's refusal to**
2122 **participate in research is always respected, unless, in exceptional**
2123 **circumstances, there is no reasonable medical alternative and local**
2124 **law permits overriding the objection; and,**
2125 – **in cases where prospective subjects lack capacity to consent,**
2126 **permission is obtained from a responsible family member or a**
2127 **legally authorized representative in accordance with applicable law.**
2128
2129

2130 ***Commentary on Guideline 15***

2131

2132 *General considerations.* Most individuals with mental or behavioural disorders are
2133 capable of giving informed consent; this Guideline is concerned only with those who
2134 are not capable or who because their condition deteriorates become temporarily
2135 incapable. The investigator must obtain the approval of an ethical review committee
2136 to include such persons in research. They should never be subjects of research that
2137 might equally well be carried out on persons in full possession of their mental
2138 faculties, but they are clearly the only subjects suitable for a large part of research into
2139 the origins and treatment of certain severe mental or behavioural disorders.

2140

2141 *Consent of the individual in studies for which competent subjects' consent is required.*

2142 The willing cooperation of persons whose mental and behavioural condition interferes
2143 with their ability to consent should be sought to the extent that their mental state
2144 permits, and any objection on their part to taking part in any study that has no
2145 components designed to benefit them directly should always be respected. The
2146 objection of such an individual to an investigational intervention intended to be of
2147 therapeutic benefit should be respected unless there is no reasonable medical
2148 alternative and local law permits overriding the objection.

2149

2150 *Permission of a surrogate for a subject incapable of giving informed consent.* The
2151 investigator must obtain the permission of a surrogate in accordance with local laws
2152 or established procedures in all studies for which individual consent would be
2153 required from subjects capable of giving consent (see Guideline 4). The permission of
2154 an immediate family member or other person with a close personal relationship with
2155 the individual should be sought, but it should be recognized that these proxies may
2156 have their own interests that may call their permission into question. Some relatives
2157 may not be primarily concerned with protecting the rights and welfare of the patients.
2158 Moreover, a close family member or friend may wish to take advantage of a research
2159 study in the hope that it will succeed in “curing” the condition. Some jurisdictions do
2160 not permit third-party permission for subjects lacking capacity to consent. Legal
2161 authorization may be necessary to involve in research an individual who has been
2162 committed to an institution by a court order.

2163

2164 *Serious illness in persons who because of mental or behavioural disorders are unable*
2165 *to give adequately informed consent.* Persons who because of mental or behavioural
2166 disorders are unable to give adequately informed consent and who have, or are at risk
2167 of, serious illnesses such as HIV infection, cancer or hepatitis should not be deprived
2168 of the possible benefits of investigational drugs, vaccines or devices that show
2169 promise of therapeutic or preventive benefit, particularly when no superior or
2170 equivalent therapy or prevention is available. Their entitlement to access to such
2171 therapy or prevention is justified ethically on the same grounds as is such entitlement
2172 for other vulnerable groups.

2173 Persons who are unable to give adequately informed consent by reason of
2174 mental or behavioural disorders are, in general, not suitable for participation in formal
2175 clinical trials except those trials that are designed to be responsive to their particular
2176 health needs and can be carried out only with them.

2177

2178 (See also Guidelines 8, 9 and 13.)

2179

2180

2181

2182

2183 **Guideline 16**

2184 **Women as research participants**

2185

2186 **Investigators, sponsors or ethical review committees should not exclude**
2187 **women of reproductive age from epidemiological research. The potential for**
2188 **becoming pregnant during a study should not, in itself, be used as a reason for**
2189 **precluding or limiting participation. However, a thorough discussion of risks to**
2190 **the pregnant woman and to her fetus is a prerequisite for the woman's ability**
2191 **to make a rational decision to enrol in an interventional study. In this**
2192 **discussion, if participation in the research might be hazardous to a fetus or a**
2193 **woman if she becomes pregnant, the sponsors/investigators should guarantee**
2194 **the prospective subject a pregnancy test and access to effective contraceptive**
2195 **methods before the research commences. Where such access is not possible,**
2196 **for legal or religious reasons, investigators should not recruit for such**
2197 **possibly hazardous research women who might become pregnant.**

2198

2199 **Commentary on Guideline 16**

2200

2201 Women in most societies have been discriminated against with regard to their
2202 involvement in research. Women who are biologically capable of becoming pregnant
2203 have been customarily excluded from formal clinical trials of drugs, vaccines and
2204 medical devices owing to concern about undetermined risks to the fetus.

2205 Consequently, relatively little is known about the safety and efficacy of most drugs,
2206 vaccines or devices for such women, and this lack of knowledge can be dangerous.

2207 A general policy of excluding from research women biologically capable of
2208 becoming pregnant is unjust in that it deprives women as a group of the benefits of the
2209 new knowledge derived from such studies. Further, it is an affront to their right of
2210 self-determination. It is particularly important that occupations that predominantly
2211 involve women workers are not excluded from epidemiological research on potential
2212 occupational hazards. Nevertheless, when given the opportunity to participate in
2213 research that could pose risks to the fetus, women of childbearing age should be
2214 helped to understand that such risk would arise if they become pregnant during the
2215 research.

2216 Although this general presumption favours the inclusion of women in research,

2217 it must be acknowledged that in some parts of the world women are vulnerable to
2218 neglect or harm in research because of their social conditioning to submit to authority,
2219 to ask no questions, and to tolerate pain and suffering. When women in such
2220 situations are potential subjects in research, investigators need to exercise special care
2221 in the informed consent process to ensure that they have adequate time and a proper
2222 environment in which to take decisions on the basis of clearly given information.

2223

2224 *Individual consent of women:* In research involving women of reproductive age,
2225 whether pregnant or non-pregnant, only the informed consent of the woman herself is
2226 required for her participation. In no case should the permission of a spouse or partner
2227 replace the requirement of individual informed consent. If women wish to consult
2228 with their husbands or partners or seek voluntarily to obtain their permission before
2229 deciding to enrol in research, that is not only ethically permissible but in some
2230 contexts highly desirable. A strict requirement of authorization of spouse or partner,
2231 however, violates the substantive principle of respect for persons.

2232 A thorough discussion of risks to the pregnant woman and to her fetus is a
2233 prerequisite for the woman's ability to make a rational decision to enrol in a study.
2234 For women who are not pregnant at the outset of a study but who might become
2235 pregnant while they are still subjects, the consent discussion should include
2236 information about the alternative of voluntarily withdrawing from the study and,
2237 where legally permissible, terminating the pregnancy. Also, if the pregnancy is not
2238 terminated, they should be guaranteed a medical follow-up.

2239

2240 (See also Guideline 17.)

2241

2242

Guideline 17

2243

Pregnant women as research participants

2244

2245 **Pregnant women should be presumed to be eligible for participation in**
2246 **epidemiological research. Investigators and ethical review committees should**
2247 **ensure that prospective subjects who are pregnant are adequately informed**
2248 **about the risks and benefits to themselves, their pregnancies, the fetus and**
2249 **their subsequent offspring, and to their fertility.**

2250

2251 **Interventional studies should be performed in this population only if it is**
2252 **relevant to the particular health needs of a pregnant woman or her fetus, or to**
2253 **the health needs of pregnant women in general, and, when appropriate, if it is**
2254 **supported by reliable evidence from animal experiments, particularly as to**
2255 **risks of teratogenicity and mutagenicity.**

2256

2257 ***Commentary on Guideline 17***

2258

2259 The justification of research involving pregnant women is complicated by the fact that
2260 it may present risks and potential benefits to two beings—the woman and the fetus—as
2261 well as to the person the fetus is destined to become. Even when evidence concerning
2262 risks is unknown or ambiguous, the decision about acceptability of risk to the fetus
2263 should be made by the woman as part of the informed consent process. Though this
2264 decision should be made by the mother, it is desirable in research directed at the
2265 health of the fetus to obtain the father’s opinion as well, when possible.

2266 Especially in communities or societies in which cultural beliefs accord more
2267 importance to the fetus than to the woman’s life or health, women may feel
2268 constrained to participate, or not to participate, in research. Special safeguards should
2269 be established to prevent undue inducement to pregnant women to participate in
2270 research in which interventions hold out the prospect of direct benefit to the fetus.
2271 Where fetal abnormality is not recognized as an indication for abortion, pregnant
2272 women should not be recruited for research in which there is a realistic basis for
2273 concern that fetal abnormality may occur as a consequence of participation as a
2274 subject in research.

2275 Investigators should include in protocols on research on pregnant women a plan
2276 for monitoring the outcome of the pregnancy with regard to both the health of the
2277 woman and the short-term and long-term health of the child.

2278

2279 (See also Commentary on Guidelines 14 and 16.)

2280

2281 **Guideline 18**

2282 **Safeguarding confidentiality**

2283

2284 **A healthcare provider should not submit any identifiable data about a patient to**
2285 **an investigator or to a database unless the patient permits such submission of**
2286 **data or it is authorized or mandated by law. The custodian of a database, and**
2287 **an investigator who receives data for research, must establish secure**
2288 **safeguards for the confidentiality of the data. Subjects should be told the**
2289 **limits, legal or other, to the investigators' ability to safeguard confidentiality**
2290 **and the possible consequences of breaches of confidentiality”.**

2291

2292 **Commentary on Guideline 18**

2293

2294 In addition to the requirements set forth in this Guideline, a growing body of laws
2295 have been adopted in many countries establishing detailed legal requirements
2296 regarding the protection of the confidentiality and security of health-related data.

2297

2298 *Confidentiality between investigator and subject.* Research relating to individuals and
2299 groups may involve the collection and storage of information that, if disclosed to third
2300 parties, could cause harm or distress. Investigators should arrange to protect the
2301 confidentiality of such information by, for example, omitting information that might
2302 lead to the identification of individual subjects, limiting access to the information,
2303 anonymizing data, or other means. During the process of obtaining informed consent
2304 the investigator should inform the prospective subjects about the precautions that will
2305 be taken to protect confidentiality.

2306

2307 The obligation to preserve confidentiality of research data encompasses all
2308 identifying information because the disclosure of such information can cause
2309 physical, psychological, social or economic harm to individuals, couples, families or
2310 other social groups or infringe their intimacy. One way of achieving confidentiality is
2311 to use only unidentifiable data; for instance, when testing unlinked anonymous blood
2312 samples for HIV infection or when unlinked anonymized or already partially
2313 aggregated data are provided by existing registries (e.g., of deaths) to the
epidemiologist for descriptive studies.

2314 When linked data and samples are used, epidemiologists customarily discard
2315 personal identifying information when consolidating data for purposes of statistical
2316 analysis; this also occurs when investigators have linked different sets of data
2317 regarding individuals with the consent of individual subjects. When personal
2318 identifiers remain on records used for a study, investigators should explain to ethical
2319 review committees why this is necessary and how confidentiality will be protected.

2320 Participation in HIV/AIDS drug and vaccine trials may impose upon the
2321 research subjects significant associated risks of social discrimination or harm; such
2322 risks merit consideration equal to that given to adverse medical consequences of the
2323 drugs and vaccines. Efforts must be made to reduce their likelihood and severity. For
2324 example, subjects in vaccine trials must be enabled to demonstrate that their HIV
2325 seropositivity is due to their having been vaccinated rather than to natural infection.
2326 This may be accomplished by providing them with documents attesting to their
2327 participation in vaccine trials, or by maintaining a confidential register of trial
2328 subjects, from which information can be made available to outside agencies at a
2329 subject's request.

2330

2331 *Limits of confidentiality.* Prospective subjects should be informed of limits to the
2332 ability of investigators to ensure strict confidentiality and of the foreseeable adverse
2333 consequences of breaches of confidentiality. Some jurisdictions require the reporting
2334 to appropriate agencies of, for instance, certain communicable diseases or evidence of
2335 child abuse or neglect. Health authorities may have the legal right to inspect study
2336 records, and a sponsor's compliance audit staff may require and obtain access to
2337 confidential data. Although employers should be informed of occupational health
2338 study findings only at the group level, the risk exists, particularly in small
2339 organizations, that the employer will be able to identify the subjects. Pooling data
2340 from a number of comparable organizations may reduce—but not completely
2341 foreclose—this risk. Conversely, research that links data from different sources (e.g.,
2342 health records, employment records, etc.) may increase the risk that individuals can be
2343 identified. These and similar limits to the ability to maintain confidentiality should be
2344 anticipated and disclosed to prospective subjects (see Guideline 5, #15).

2345

2346 *Data security.* Study materials and databases may contain data which besides being
2347 confidential also need to be ensured long life spans, which may in extreme cases
2348 cover several generations. Standards and methods need to be developed for the secure
2349 preservation of data that are, or could be, held for longitudinal studies. Investigators
2350 are responsible for ensuring data security and legitimate access to data by protecting
2351 them against physical injury, criminal action and during any change which may be
2352 associated with changes of technical systems. Several general principles are useful in
2353 judging the adequacy of data protection:

2354

- 2355 • Plans for data protection and custody of data, copies and backup facilities,
2356 whether in the hands of an institution or an individual investigator, should be
2357 outlined in the research plan and reviewed by the ethical review committee.
- 2358 • Limitations on access and legal requirements for disclosure, if any, should be
2359 clearly outlined in the research plan.
- 2360 • The level of identifiability should be appropriate to the scientific goals of the
2361 research, as well as appropriate to adequately protecting research subjects.
- 2362 • The informed consent process should include a description of how data and/or
2363 samples will be handled and who will have access; when there will be different
2364 levels of data protection, the information should be explicit about this, explaining
2365 in general terms the modes of protection at each level.

2366

2367 *Confidentiality between physician and patient.* Physicians and other health care
2368 professionals record the details of their observations and interventions in medical
2369 records. Patients have the right to expect that these health-care professionals will hold
2370 all information about them in strict confidence and disclose it only to those who need,
2371 or have a legal right to, the information, such as other attending physicians, nurses, or
2372 other health-care workers who perform tasks related to the diagnosis and treatment of
2373 patients.

2374 The use of such records in epidemiological studies without the informed consent of
2375 the patients concerned may be approved by an ethical review committee when this is

2376 consistent with the requirements of applicable law and with the conditions discussed
2377 in the Commentary on Guideline 4, and provided that there are secure safeguards of
2378 confidentiality; information may also be provided without patient consent to a register
2379 or database when authorized or mandated by law. Access by researchers to patients'
2380 medical records must be approved in advance by an ethical review committee and
2381 supervised by a person who is fully aware of the confidentiality requirements. When
2382 the practice of collecting patient records for use in research without informed consent
2383 has been approved in a particular setting (such as a hospital or a clinic), patients
2384 should be notified of this practice; notification is usually by means of a statement in
2385 patient-information brochures. It should be made clear to persons that they have an
2386 option to restrict the secondary, research uses of information that is submitted for
2387 billing, prescribing, or other purposes and that if they choose to do so, the care
2388 provided will not be affected.

2389 For populations covered by automated health databases, an ethical review
2390 committee with expertise regarding the scope of access researchers will have to the
2391 medical information and the types of research they want to conduct should ensure that
2392 confidentiality rules and procedures are in place and certify the public health value of
2393 the research (e.g., the Data Access Review Committee for the Canadian Saskatchewan
2394 Health database, the Scientific and Ethical Advisory Group for the UK General
2395 Practice Research Database). The ethical review committee should also determine
2396 how patients should be advised of such practices, usually by means of a statement in
2397 patient-information brochures, and the ethical or legal need to provide patients with
2398 the choice to “opt out” of secondary use of certain parts of their medical record.

2399 When already existing collections of medical records that were assembled and
2400 stored without an explicit notification and consent procedure (including an

2401 opportunity to “opt out”) offer important and otherwise unobtainable data, an ethical
2402 review committee needs to decide whether the use of such records is justified.
2403 Arguments pertaining to this decision are discussed within the more general
2404 framework of the waiving of consent in the Commentary on Guideline 4, under the
2405 section "*Waiver of consent requirements.*"

2406

2407 *Disclosure of test results to individuals.* When genetic or other diagnostic tests will be
2408 reported to the subject or to the subject’s physician, the subject should be informed that such
2409 disclosure will occur and that the samples to be tested will be clearly labeled. Investigators
2410 should not disclose results of such diagnostic tests to relatives of subjects without the
2411 subjects’ consent. In places where immediate family relatives would usually expect to be
2412 informed of such results, the research protocol, as approved or cleared by the ethical review
2413 committee, should indicate the precautions in place to prevent such disclosure of results
2414 without the subjects’ consent; such plans should be clearly explained during the process of
2415 obtaining informed consent.

2416

2417 *Issues of confidentiality in genetic research.* An investigator who proposes to perform
2418 genetic tests of known clinical or predictive value on biological samples that can be
2419 linked to an identifiable individual must obtain the informed consent of the individual
2420 or, when indicated, the permission of a legally authorized representative. (Issues
2421 raised by research on stored samples are addressed in Guideline 24 and the associated
2422 Commentary.)

2423

2424 *Special confidentiality issues for groups in genetic research.* When unidentifiable
2425 biological samples (that is, those that have been fully anonymized and unlinked) are
2426 used in genetic research in a specific population or community, the results obtained
2427 cannot be fed back to individual participants, but in such cases research findings and
2428 advice to the relevant group may be communicated by suitable means. These

2429 processes should be fully explained to the prospective subjects as part of informed
2430 consent (see Guideline 5).

2431 Epidemiologists and ethical review committees should however be aware that,
2432 under specific circumstances, the genetic information gathered in a study (on
2433 pharmacogenetics or pharmacogenomics, for example) may have a significant impact
2434 on the subject and his/her family extending over generations, and in some instances
2435 on the whole population group to which the subject concerned belongs.

2436 With genetic population studies, the possibility of new forms of discrimination
2437 based on genotype may emerge. If genetic variations in certain diseases or conditions
2438 are significantly more common in a particular community or ethnic group, this
2439 information may result in stigmatization and stereotyping and in discrimination in
2440 health care services or in the fields of life insurance, employment, reproductive rights,
2441 etc. The importance of confidentiality is heightened when genetic information might
2442 be used to discriminate or infringe the human rights, fundamental freedoms or dignity
2443 of individuals, families, groups or communities (see Guideline 8).

2444

2445

Guideline 19

2446 ***Right of injured subjects to treatment and compensation***

2447

2448 **Investigators should ensure that research subjects who suffer injury as a**
2449 **result of their participation are entitled to free medical treatment for such injury**
2450 **and to such financial or other assistance as would compensate them equitably**
2451 **for any resultant impairment, disability or handicap. In the case of death as a**
2452 **result of their participation, their dependants are entitled to compensation.**
2453 **Subjects must not be asked to waive the right to compensation.**

2454

2455 ***Commentary on Guideline 19***

2456

2457 Guideline 19 is concerned with two distinct but closely related entitlements. The
2458 first is the uncontroversial entitlement to free medical treatment and compensation for
2459 accidental injury inflicted by procedures or interventions performed exclusively to
2460 accomplish the purposes of research (non-therapeutic procedures). The second is the
2461 entitlement of dependants to material compensation for death or disability occurring

2462 as a direct result of study participation. Implementing a compensation system for
2463 research-related injuries or death is likely to be complex, however.

2464

2465 *Equitable compensation and free medical treatment.* Compensation is owed to
2466 research subjects who are disabled as a consequence of injury from procedures
2467 performed solely to accomplish the purposes of research. Compensation and free
2468 medical treatment are generally not owed to research subjects who suffer expected or
2469 foreseen adverse reactions to investigational therapeutic, diagnostic or preventive
2470 interventions when such reactions are not different in kind from those known to be
2471 associated with established interventions in standard medical practice.

2472 The ethical review committee should determine in advance: i) the injuries for
2473 which subjects will receive free treatment and, in case of impairment, disability or
2474 handicap resulting from such injuries, be compensated; and ii) the injuries for which
2475 they will not be compensated. Prospective subjects should be informed of the
2476 committee's decisions, as part of the process of informed consent. As an ethical
2477 review committee cannot make such advance determination in respect of unexpected
2478 or unforeseen adverse reactions, such reactions must be presumed compensable and
2479 should be reported to the committee for prompt review as they occur.

2480 Subjects must not be asked to waive their rights to compensation or required to
2481 show negligence or lack of a reasonable degree of skill on the part of the investigator
2482 in order to claim free medical treatment or compensation. The informed consent
2483 process or form should contain no words that would absolve an investigator from
2484 responsibility in the case of accidental injury, or that would imply that subjects would
2485 waive their right to seek compensation for impairment, disability or handicap.
2486 Prospective subjects should be informed that they will not need to take legal action to
2487 secure the free medical treatment or compensation for injury to which they may be
2488 entitled. They should also be told what medical service or organization or individual
2489 will provide the medical treatment and what organization will be responsible for
2490 providing compensation.

2491

2492 *Obligation of the sponsor with regard to compensation.* Before the research begins,
2493 the sponsor, whether a pharmaceutical company or other organization or institution,
2494 or a government (where government insurance is not precluded by law), should agree

2495 to provide compensation for any physical injury for which subjects are entitled to
2496 compensation, or come to an agreement with the investigator concerning the
2497 circumstances in which the investigator must rely on his or her own insurance
2498 coverage (for example, for negligence or failure of the investigator to follow the
2499 protocol, or where government insurance coverage is limited to negligence). In certain
2500 circumstances it may be advisable to follow both courses. Sponsors should seek
2501 adequate insurance against risks to cover compensation, independent of proof of fault.

2502

2503

Guideline 20

2504

Strengthening capacity for ethical and scientific review

2505

and epidemiological research

2506

2507

Many countries lack the capacity to assess or ensure the scientific quality or

2508

ethical acceptability of epidemiological research proposed or carried out in

2509

their jurisdictions. In externally sponsored collaborative studies, sponsors and

2510

investigators have an ethical obligation to ensure that the research projects for

2511

which they are responsible in such countries contribute effectively to national

2512

or local capacity to design and conduct epidemiological research, and to

2513

provide scientific and ethical review and monitoring of such research.

2514

2515

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

2516

2517

- **establishing and strengthening independent and competent ethical review processes/ committees**

2518

2519

2520

- **strengthening research capacity**

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- **developing technologies appropriate to public health, health care and epidemiological research**

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- **training of research and health-care staff**

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- **educating the community from which research subjects will be drawn.**

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2529 **Commentary on Guideline 20**

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2531 External sponsors and investigators have an ethical obligation to contribute to a host
2532 country's sustainable capacity for independent scientific and ethical review and
2533 epidemiological research. Strengthening capacity for conducting epidemiological
2534 research, as well as for undertaking scientific and ethical review of epidemiological
2535 projects, should be regarded as a specific need in many countries, notably because
2536 adequate capacity for biomedical research does not automatically entail adequate
2537 capacity for epidemiological research. This further extends to capacity in very
2538 specialized domains of epidemiological research such as genetic, occupational or
2539 social epidemiology.

2540 Before undertaking research in a host country with little or no such capacity,
2541 external sponsors and investigators should include in the research protocol a plan that
2542 specifies the contribution they will make. The amount of capacity building reasonably
2543 expected should be proportional to the magnitude of the research project. A brief
2544 epidemiological study involving only review of medical records, for example, would
2545 entail relatively little, if any, such development, whereas a considerable contribution
2546 is to be expected of an external sponsor of, for instance, a large-scale vaccine field-
2547 trial expected to last two or three years.

2548 The specific capacity-building objectives should be determined and achieved
2549 through dialogue and negotiation between external sponsors and host-country
2550 authorities. External sponsors would be expected to employ and, if necessary, train
2551 local individuals to function as investigators, research assistants or data managers, for
2552 example, and to provide, as necessary, reasonable amounts of financial, educational
2553 and other assistance for capacity-building. To avoid conflict of interest and safeguard
2554 the independence of review committees, financial assistance should not be provided
2555 directly to them; rather, funds should be made available to appropriate authorities in
2556 the host-country government or to the host research institution.

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2558 (See also Guidelines 10 and 22.)

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Guideline 21

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Ethical obligation of external sponsors

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to provide health-care services

External sponsors are ethically obliged to ensure the availability of:

- health-care services that are essential to the safe conduct of the research;**
- treatment for subjects who suffer injury as a consequence of research interventions; and,**
- services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.**

Commentary on Guideline 21

Obligations of external sponsors to provide health-care services will vary with the circumstances of particular studies and the needs of host countries. Some types of interventional epidemiological studies are intended to find out whether a screening programme for a disease may lead to an improvement in prognosis, by means of early diagnosis and treatment. The intervention cannot be limited to administering a screening test and examining whether the disease has been detected at an earlier stage than through standard clinical practice, but should also include provision of the pertinent treatment.

The sponsors' obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn, or to the host country, and for how long. In addition, investigators should specify what action if any they will take when medical conditions are detected within a study population that are not related to the study but that need treatment, for instance, obesity or hypertension when recruiting subjects in an observational cohort study of diet and cancer. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when appropriate, the community from which subjects are to be drawn. The agreed arrangements should be specified in the consent process and

2596 document.

2597 Although sponsors are, in general, not obliged to provide health-care services
2598 beyond that which is necessary for the conduct of the research, it is morally
2599 praiseworthy to do so. Such services typically include treatment for diseases
2600 contracted in the course of the study. It might, for example, be agreed to treat cases of
2601 an infectious disease contracted during a trial of a vaccine designed to provide
2602 immunity to that disease, or to provide treatment of incidental conditions unrelated to
2603 the study.

2604 The scope and limits of the obligation to ensure that subjects who suffer injury
2605 as a consequence of research interventions obtain medical treatment free of charge,
2606 and that compensation be provided for death or disability occurring as a consequence
2607 of such injury, are the subject of Guideline 19.

2608 When prospective or actual subjects are found to have diseases unrelated to the
2609 research, or cannot be enrolled in a study because they do not meet the health criteria,
2610 investigators should, as appropriate, advise them to obtain, or refer them for, medical
2611 care. In general, also, in the course of a study, sponsors should disclose to the proper
2612 health authorities information of public health concern arising from the research.

2613 The obligation of the sponsor to make reasonably available for the benefit of the
2614 population or community concerned any intervention or product developed, or
2615 knowledge generated, as a result of the research is considered in Guideline 10.

2616

2617

Guideline 22

Disclosure and review of potential conflicts of interest

2619

2620 **The investigator is responsible for ensuring that the materials submitted to an**
2621 **ethical review committee include a declaration of any potential conflicts of**
2622 **interest affecting the study. Ethical review committees should develop forms**
2623 **that facilitate the reporting of such potential conflicts and materials explaining**
2624 **their use for investigators. Ethical review committees should evaluate each**
2625 **study in the light of any declared conflicts and ensure that appropriate means**
2626 **of mitigation are provided. If a potentially serious conflict of interest cannot be**
2627 **adequately mitigated, the committee should not approve the project.**

2628

2629 **Commentary on Guideline 22**

2630

2631 *Types of conflicting interests.* Conflicts can arise from a sponsor's interest in the
2632 study's outcome; such interests include those of a health ministry or other public
2633 agency and are not limited to commercial sponsors. Such conflicts may include a
2634 financial stake held by the investigator or senior members of the research team (as
2635 well as their close family members) in the sponsor of the research (such as an equity
2636 interest), payments to the investigator that depend on the rapidity with which subjects
2637 are recruited or certain results reported, restrictions on the investigator's freedom to
2638 analyze the data or publish research results, or dependence of a research centre on
2639 substantial, ongoing support from a particular sponsor, private or public.

2640

2641 *Potential conflicts of interest related to project support.* Epidemiological studies may
2642 receive funding from commercial firms. Such sponsors have good reason to support
2643 research methods that are ethically and scientifically acceptable, but cases have arisen
2644 in which the conditions of funding may have introduced bias. For example,
2645 investigators have sometimes had little or no input into study design, limited access to
2646 the raw data, or limited participation in data interpretation, and the results of some
2647 studies have not been published when they were unfavourable to the sponsor's
2648 product. (This risk of bias may also arise with other sources of support, such as
2649 government or foundations.) As the persons directly responsible for their work,
2650 investigators should not enter into agreements that interfere unduly with their access
2651 to the data or their ability to analyze the data independently, prepare manuscripts, or
2652 publish them. Investigators must also disclose potential or apparent conflicts of
2653 interest on their part to the ethical review committee or to other institutional
2654 committees designed to evaluate and manage such conflicts. Ethical review
2655 committees should therefore ensure that these conditions are met (see also the
2656 Commentary on Guideline 2, *Multi-centre research*).

2657

2658 *Institutional conflicts.* Officials overseeing research also need to be aware of – and, as
2659 necessary, take steps to mitigate – institutional conflicts of interest which may arise
2660 when a research centre derives substantial support (perhaps covering years of
2661 funding) from a single sponsor or handful of sponsors; in such circumstances, it may

2662 be difficult for persons acting on behalf of the organization, including members of the
2663 ethical review committee, to reach judgments adverse to the sponsor's interests or
2664 wishes. The fact that the ethical review committee (or the institution where it
2665 operates) is paid a fee for reviewing a study does not present an inherent conflict of
2666 interest, provided that the fee is reasonably related to the costs of conducting the
2667 review, is not dependent on the outcome of the review, is uniform for all projects of
2668 comparable complexity, and is set and negotiated by persons other than those actually
2669 engaged in the ethical review process.

2670

2671 *Standardized disclosure.* Investigators will most likely come to recognize potential
2672 conflicts of interest if they are prompted to scrutinize research sponsorship as an
2673 expected part of preparing a description of their projects for the ethical review
2674 committee. Thus, the development of a standardized disclosure form and related
2675 educational and explanatory materials (by a committee or group of committees, such
2676 as a research ethics association) is recommended as a good way to ensure that
2677 investigators understand the potential for conflicts of interest and routinely report
2678 relevant facts about their own studies to review committees and in all publications. It
2679 is important that such a document provide a definition of potential conflict of interest.
2680 The explanatory materials should also help investigators to understand that a potential
2681 conflict of interest is not necessarily disqualifying but may be managed either through
2682 disclosure (both before the study, in consent materials, and when any results are
2683 reported) or other means.

2684

2685 *Mitigation of conflicts.* The means that ethical review committees may wish to
2686 consider for mitigating conflicts of interest include an agreed process for peer review
2687 of the study design, analysis, results, and interpretation; guarantees of the
2688 investigator's right to determine the scientific design and to use the data and publish
2689 results, free of undue restrictions from the sponsor; the existence of multiple sources
2690 of support for the study; etc. When appropriate, the committee may also require that
2691 potential conflicts of interest be part of the information provided in seeking subjects'
2692 consent to participate, beyond describing "the nature and sources of funding for the
2693 research", which is an element of informed consent under Guideline 5.

2694

2695

Guideline 23

2696

Use of the Internet in epidemiological research

2697

2698 **If the Internet is used as a tool to identify respondents or to collect data in**
2699 **epidemiological research, the investigator must ensure that an appropriate**
2700 **informed consent procedure is applied and that data confidentiality is**
2701 **maintained.**

2702

Commentary on Guideline 23

2704

2705 There are several ways in which researchers can use the Internet while performing
2706 epidemiological research. First, while collecting data, researchers may use the Internet
2707 to actually perform the research itself (online research); visitors to sites may be
2708 enrolled as respondents and questionnaires may be made accessible through the
2709 Internet. In open Internet locations, investigators may observe, as a source of data,
2710 what others are saying and doing without necessarily interacting directly with other
2711 visitors to the site in question. (Such virtual “spaces” are public but may be regarded
2712 as private by users who are not adequately attentive to the ability of observers to
2713 “participate” invisibly.) Second, the Internet plays an increasingly important role for
2714 researchers in building databases; researchers may send electronic files containing the
2715 results of their research to other researchers for collaborative purposes or to aid in the
2716 construction of a centralized repository on information on a particular topic. This is
2717 the case, for instance, in multi-centre trials. Finally, after completion of the study,
2718 researchers may want to make some results available through the Internet. The
2719 principles of scientific validity of the study, informed consent, confidentiality, and
2720 balancing of potential benefit and harm are generally applicable to all of these uses of
2721 the Internet, but research using the Internet can have several unique features.

2722

2723 *Using the Internet to collect data and build databases.* Subjects’ privacy,
2724 confidentiality and security are at stake when research is conducted through the
2725 Internet. Researchers should be explicit about their presence while doing online
2726 research and seek the informed consent of participants. As part of the informed
2727 consent process, participants should be informed of the means and degree of

2728 protection applied to the data as well as where the data and their backup will be
2729 stored, for how long and who will have access to them. As no face-to-face contact
2730 takes place between participants and investigators, subjects' agreement to participate
2731 should be based on a clear disclosure of the purposes for which data are being
2732 collected and who (investigator and institution) is collecting or accessing them; the
2733 investigator is responsible for maintaining records that document informed consent.
2734 (see also Guideline 6)

2735 Subjects' privacy, confidentiality and security are at stake when data are
2736 conveyed to others electronically. Researchers should make sure that confidentiality
2737 of information is guaranteed during data collection, transfer to other centres and the
2738 building of a common database. Registration forms and questionnaires with personal
2739 identifiers should receive a high degree of security. Passwords and the best available
2740 technology, such as encryption, should be used in order to make sure that only
2741 authorized persons are able to read the data.

2742

2743 *Results made available on the Internet.* After completion of a study, the accuracy and
2744 completeness of the information made available on the Internet become relevant.
2745 Researchers should be explicit in indicating whether the information provided is
2746 preliminary or definitive, and how complete it is.

2747

2748 *Electronic collection of health-related data through new technologies.* Subjects'
2749 privacy, confidentiality and security are also at stake when data are collected through
2750 electronic devices carried by or implanted in individuals. Epidemiological studies
2751 using such methods must attend to the resulting issues.

2752

2753

Guideline 24

2754

Use of stored biological samples and related data

2755

2756 **When collecting and storing human biological samples (and related data, such**
2757 **as health or employment records) for future epidemiological research, the**
2758 **investigator must obtain the voluntary informed consent of the individual**
2759 **donor or, in the case of an individual who is not capable of giving informed**
2760 **consent, the permission of a legally authorized representative in accordance**

2761 **with applicable law. The consent should specify: the conditions and duration**
2762 **of storage; who will have access to the samples; the foreseeable uses of the**
2763 **samples, whether limited to an already fully defined study or extending to a**
2764 **number of wholly or partially undefined studies; and the intended goal of such**
2765 **use, whether only for research, basic or applied, or also for commercial**
2766 **purposes. The ethical review committee should satisfy itself that the proposed**
2767 **collection and storage protocol and the consent procedure meet these**
2768 **specifications.**

2769

2770 **The protocol of every study using stored human biological samples (and**
2771 **related data) must be submitted to an ethical review committee, which should**
2772 **satisfy itself that the proposed use of the samples comes within the scope**
2773 **specifically agreed to by the subjects.**

2774

2775 **For stored samples collected for past research, clinical or other purposes**
2776 **without informed consent to their use for research, the ethical review**
2777 **committee may consider waiving the consent if it proves materially unfeasible**
2778 **to obtain it, provided that it concludes that doing so would not harm the rights**
2779 **or welfare of the persons from whom the samples were collected.**

2780

2781 ***Commentary on Guideline 24***

2782

2783 Epidemiologists have long analyzed biological samples and are now increasingly
2784 using the tools of molecular genetics to understand the interaction of factors that
2785 contribute to disease. When combined with information from medical and other
2786 sources (such as dietary or occupational records), data from biological samples
2787 provide a powerful tool in deciphering the role of environmental and genetic factors
2788 in human health and disease. Consent to the use of samples collected and immediately
2789 analyzed for the purpose of a specific epidemiological study come under Guideline 4
2790 and has been discussed in the Commentary on that Guideline.

2791 Particular issues arise, however, for the use of stored samples, repositories of
2792 which are fast multiplying as a key resource for research, including in particular in the
2793 field of epidemiology. These issues are different in degree, if not in nature, from those
2794 concerning the use solely of recorded data, such as medical records. While from the

2795 latter it is only possible to generate new information by linking different recorded
2796 data, for instance drug use with a subsequent health outcome, analytical
2797 determinations of all kinds carried out on biological samples can generate new data,
2798 and consequently new information, in a virtually limitless amount.

2799 This inherent information-generating potential requires that strict measures be
2800 taken, to the satisfaction of the ethical review committee examining the protocol for
2801 establishment and management of a repository, for assuring not only the physical
2802 protection and maintenance of the samples but also appropriate confidentiality of the
2803 link between biological specimens and personal identifiers of the donating subjects.
2804 This responsibility falls upon the custodian of the repository. It is the responsibility of
2805 the person who obtains and submits the sample to a repository (e.g., a physician in the
2806 course of a diagnostic or screening procedure, or an epidemiologist in the course of a
2807 field study) to ensure that donors whose samples and related data will be stored have
2808 been informed about the potential future uses of such material, and that the samples
2809 will be stored and made available in accordance with conditions explicitly agreed by
2810 them (see Guideline 5, points 18-20). The informed consent should be reviewed and
2811 approved by the ethical review committee responsible for the repository, in addition
2812 to any review required by an ethical review committee at the institution where the
2813 samples are collected.

2814 Three sources of stored samples are commonly in use:

- 2815 a. repositories of samples collected and stored with informed consent for long-
2816 term, epidemiological studies (for example, so-called "population biobanks");
- 2817 b. repositories of samples collected and stored in the context of a specific
2818 research [without explicit and fully-informed consent (in line with practices
2819 prevailing at the time)];
- 2820 c. repositories of samples (typically surgically excised tissues, bioptic
2821 fragments, and leftover blood collected for diagnostic purposes) collected and
2822 stored in the context of routine clinical care or pathological or forensic
2823 examination.

2824

2825 *a. Repositories of samples collected at present and stored for long-term,*
2826 *epidemiological studies.* The value of repositories for longitudinal studies of specific
2827 diseases is now widely recognized; likewise, several large population biobanks are

2828 being established to allow studies across many diseases, through correlations of
2829 genetic, environmental, occupational, and other health data. Such repositories share an
2830 important characteristic: the persons whose samples are stored explicitly agree to this
2831 future use through an informed consent procedure approved by an ethical review
2832 committee. However, since such future research inherently involves the testing of as-
2833 yet unformulated hypotheses and the carrying out of analytical determinations
2834 unforeseeable at the time samples are collected, the information disclosed must of
2835 necessity lack much of the specificity usually expected in an acceptable informed
2836 consent process.

2837 The ideal and most direct way out of this dilemma is to seek from the
2838 participants a new consent each time a new hypothesis is going to be tested, a
2839 procedure which, though cumbersome, may be feasible in studies where participants
2840 are contacted and followed up at regular intervals (say, every one or two years). Even
2841 this procedure, however, leaves out people who die in the interval, a feature that may
2842 seriously bias the study results; it will be up to the ethical review committee, notably
2843 in the light of the response obtained from the subjects who are actually requested to
2844 give a new consent, to advise for or against the use of the samples from deceased
2845 persons. A second best approach is to make the consent given at enrolment specific
2846 enough regarding the type of factors and health endpoints to be investigated in the
2847 future (even if any actual hypotheses cannot be indicated, being as yet unknown) to
2848 constitute the basis for a genuinely "informed" agreement on the part of donors. This
2849 solution may be the only practicable one in studies where subjects are "passively"
2850 followed up, for instance through disease registries, but are not contacted by the
2851 investigators. A third conceivable solution would be consent to an open-ended
2852 donation of the sample to be used for biomedical and epidemiological research,
2853 conditional upon the approval of an ethical review committee. This solution is highly
2854 debatable and [likely to be] unacceptable under the ethical standards applied in
2855 several countries. It may also be deceptively simple because it implies that, in order to
2856 give a current informed consent, the participant should in any case be made aware
2857 (unless he/she explicitly refuses) of the spectrum of studies that the blanket formula
2858 "biomedical or epidemiological research" encompasses and which kind of studies, if
2859 any, it excludes.

2860 In no case can a clearance given by an ethical review committee to establish a

2861 repository also be regarded as a clearance to carry out an actual study using the
2862 samples in the repository; a new clearance is required after scientific and ethical
2863 review of every specific study protocol.

2864 Especially in the context of repositories established for longitudinal study of a
2865 particular disease, the informed consent should clearly stipulate what return of
2866 information—if any—derived from analysis of the samples is foreseen, should the
2867 subject so wish. In general, information of uncertain scientific validity or meaning
2868 would not qualify for transmission to the participant. It may also be reasonable to
2869 consider not all health-related information generated by the investigations conducted
2870 on the biological samples but only information potentially beneficial to the subject
2871 and/or his/her relatives, for example diagnostic information on gene variants or
2872 phenotypic traits established as relevant to health, particularly when amenable to
2873 some form of beneficial intervention or information on markers of an infectious
2874 disease or of a harmful environmental exposure, especially if avoidable.

2875

2876 *b. Repositories of samples collected and stored in the past with no informed consent*
2877 *in the context of research.* When already existing repositories of biological samples
2878 collected and stored without an explicit consent procedure offer important and
2879 otherwise unobtainable data, an ethical review committee needs to decide whether the
2880 use of such samples is justified in the absence of explicit consent. Arguments
2881 pertaining to this decision are discussed within the more general framework of
2882 waiving of consent in the Commentary on Guideline 4, under the section "*Waiver of*
2883 *consent requirements*".

2884

2885 *c. Repositories of routinely collected samples.* Secondary use of samples collected in
2886 the context of clinical or preventive (screening) practice does not raise ethical
2887 objections if the informed consent by the patient makes clear that samples can also be
2888 used in the future for research purposes, provided these are explicitly specified. Given
2889 the likelihood that such materials will be of interest to future researchers, it would be
2890 good clinical practice to insist that patients always be offered several options: to have
2891 their samples used only for their own treatment or benefit and then discarded; to allow
2892 stored samples to be used for research directly related to the condition for which they
2893 have been treated; or to allow stored samples to be used for unrelated research, with

2894 or without personal identifiers (as noted above, this blanket option would be
2895 unacceptable under the ethical standards applied in several countries). These options
2896 may be presented during a conversation with the patient or in an information
2897 document upon admittance to the hospital. It should be made clear to persons, that it
2898 is reasonable to choose to "opt out" and that such a choice will not adversely affect
2899 the care provided to them. (Of course, if the person allows future studies using
2900 identifiable samples which then generates new information of definite clinical value
2901 to that person, ordinary good practice dictates that the person be contacted again even
2902 if years have elapsed in between). In any case, the person should be told that any
2903 research uses of the stored samples will be subject to approval by the relevant ethical
2904 review committee. Consent for each study to be conducted with samples collected
2905 routinely without explicit consent for future research use must be sought. Only if this
2906 is unobtainable, such as if the patient proves after a reasonable attempt to contact him
2907 to be untraceable or is dead, may an ethical review committee consider the option of
2908 allowing the use of the samples for projects which cannot be carried out in alternative
2909 ways; these conditions are likely to hold, for example, for "historical" collections of
2910 samples stored when contemporary informed consent policies were not applied.

2911

2912 *Genetic research.* When individual consent or permission has not been obtained to
2913 perform a genetic test that is of known predictive value or that gives reliable
2914 information about a known heritable condition, the investigator must see that
2915 biological samples are fully anonymized and unlinked before performing the test; this
2916 ensures that no information about specific individuals can be derived from such
2917 research or passed back to them.

2918 When biological samples are not fully anonymized and when it is anticipated
2919 that there may be valid clinical or research reasons for linking the results of genetic
2920 tests to research subjects, the investigator in seeking informed consent should assure
2921 prospective subjects that their identity will be protected by secure coding of their
2922 samples (encryption) and by restricted access to the database, and should explain this
2923 process to them.

2924 (See also Guidelines 5, 6 and 7.)

2925

2926 ***Appendix 1:***

2927

2928 **Glossary**

2929

2930 This glossary defines terms used in the text of the Guidelines and Commentaries.

2931 Several definitions are based on, or adapted from, those found in John Last's

2932 *Dictionary of Epidemiology*, 4th ed. (Oxford University Press) to which the reader is

2933 more generally referred for terms encountered in epidemiological study protocols and

2934 reports. Within a definition *italicized words* refer to other terms found in the glossary.

2935

2936 **Analytic study.** An epidemiological study to test the hypothesis that a *factor* is the

2937 cause of an health effect, for instance that the *factor* causes a disease or that it

2938 prevents a disease. The commonest types of analytic studies are *case-control*, *cohort*

2939 and *cross-sectional studies*. Analytic studies are contrasted with *descriptive studies*,

2940 which do not test hypotheses. In addition to these types of studies, all of which are

2941 *observational*, analytic studies also encompass *interventional studies*.

2942

2943 **Anonymous.** A record, biological sample or item of information that in no

2944 circumstance can be linked to an identified person.

2945

2946 **Benefit.** A favourable consequence arising from a study, for example the

2947 demonstration that a vaccine is effective in a *randomized controlled trial* or the

2948 identification of a workplace hazard in an *observational study*. Benefits are often

2949 contrasted to "risks" (as in a "risk/benefit ratio") but the term "risk" is ambiguous

2950 because it connotes both an adverse consequence and the probability of its occurrence

2951 (i.e., *risk* in the formal epidemiological meaning). To avoid this ambiguity, the term

2952 "risk" is better replaced by "harm" when the consequence is certain or has already

2953 occurred, or "potential harm" when it remains a possibility. In the context of planned

2954 research, the balance to be struck is thus between potential benefits (to society and

2955 possibly to the subjects) and potential harms (principally to subjects), paying attention

2956 both to the type and magnitude of these benefits and harms and the probability that

2957 they will occur. Potential benefits and harms "to subjects" may not be restricted to

2958 them, but may extend to their family members or, more generally, to a group to which

2959 they belong. For instance, findings of a higher than average prevalence of certain
2960 genetic traits or diseases among study subjects may offer a means of early assessment
2961 and prevention (a benefit for the group of which they are a part) but may also
2962 stigmatize the family or the group in the eyes of others (a harm for the group).

2963

2964 **Case-control study.** An *observational study* comparing cases with a disease (for
2965 example, lung cancer) with non-diseased control subjects from the same population as
2966 the cases being studied. The relationship of a *factor* (for example, tobacco smoking)
2967 to the disease (here, lung cancer) is examined by comparing how frequently the *factor*
2968 or its different levels (the number of cigarette smoked) is present among cases and
2969 among controls. Information about the *factor(s)* of interest be gathered by
2970 interviewing people or by consulting existing records, for example, prescription
2971 records for a study of adverse effects of a drug.

2972

2973 **Cluster sampling.** A method of selecting subjects from a population in which each
2974 unit selected is a group of subjects (e.g., all children in a school or all people in a
2975 town district) rather than an individual. Clusters are usually selected through *random*
2976 *sampling*.

2977

2978 **Cohort study.** An *observational study* in which the occurrence of a disease or other
2979 health condition is recorded in any designated group of subjects who are followed up
2980 over a period of time, usually years or, in some studies, decades. At the start of the
2981 observation, the subjects are classified according to the *factor(s)* whose relation with
2982 the disease is being investigated. For example, blood pressure may be used to classify
2983 subjects in a study of coronary heart disease; the study would consist of comparing
2984 the frequency with which coronary heart disease occurred subsequently in subgroups
2985 of subjects with different blood pressure levels. In some cohort studies, the subjects
2986 are contacted and asked questions and/or undergo measurements and blood tests by
2987 the investigator at the time of enrolment in the cohort and at fixed intervals thereafter,
2988 while in other studies the cohort can be formed using existing records (e.g., hospital
2989 or employment records) with no technical need to contact the subjects.

2990

2991 **Competent person.** A person capable of understanding the meaning of the
2992 information she is presented with and of taking decisions based on it. Certain persons,
2993 such as children up to a specified age are typically deemed by the law to be legally
2994 incompetent, while others, including people whose mental capacity or thought
2995 processes are impaired by mental or physical illness, can be found by a court or other
2996 body to be incompetent to make some or all decisions.

2997

2998 **Control (noun and adjective).** Designates the group of subjects against which the
2999 group(s) of subjects of interest in a study are compared. For example in a *case-control*
3000 *study* the subjects with the disease of interest, say lung cancer, may be compared with
3001 subjects without the disease, the control or *reference group*, to find out whether the
3002 former were more frequently exposed than the latter to carcinogenic fumes. In a
3003 *randomized controlled trial (RCT)* of a new drug, the subjects given the intervention
3004 being studied are compared with the “control” subjects who receive a routinely used
3005 drug or, under certain circumstances, a *placebo*.

3006

3007 **Control (verb).** In public health, “to control” means to prevent a disease (or its causal
3008 factors) or to treat it .A disease which can be prevented or treated, or both, is
3009 “controllable”. In the analysis of an epidemiological study, control means to remove
3010 the influence of those factors such as age and gender that may be differently
3011 distributed in two groups of subjects which are being compared so as to avoid having
3012 those factors distort the comparison of the two groups, for instance of their respective
3013 death rates.

3014

3015 **Cross-sectional study.** An *observational study* in which the presence of a disease (or
3016 other health condition) and the presence of factor(s) of interest are simultaneously
3017 ascertained at a point in time in order to examine their relationship. The ascertainment
3018 is often carried out in random representative samples of a population. For example, a
3019 factor such as blood pressure and a health condition as defined by an
3020 electrocardiogram may be measured in subjects selected at random within each age-
3021 and sex-specific stratum of a population.

3022

3023 **Descriptive study.** An *observational study* portraying the occurrence of a disease or
3024 of other health-related events in relation to geographical areas, calendar periods and
3025 demographic characteristics of populations, such as age, sex, educational level,
3026 occupation, socioeconomic conditions, etc. These studies can be carried out as “ad
3027 hoc” research investigations or as institutional and regular activities of disease
3028 surveillance within public health practice. In both contexts they contribute to
3029 generating hypotheses on the *factors* potentially determining the observed disease
3030 patterns. These hypotheses can then be tested in *analytic studies* whose results may in
3031 turn be used to verify how much the factors account for the disease patterns.

3032 Descriptive studies usually make use of individual records as available in existing
3033 databases or registries (of deaths, of notifiable communicable diseases, of cancer, etc.)
3034 and do not require identification of the persons to whom the records belong.

3035

3036 **Factor.** Generically any event, characteristic or other definable entity potentially or
3037 actually capable of affecting health or contributing to a health-related condition.
3038 Factors include age, sex, body characteristics (such as height, weight, blood pressure,
3039 genetic traits, etc.), economic status, occupation, residence, and a wide range of
3040 personal behaviour and environmental causes external to the body including diet,
3041 drugs, etc.

3042

3043 **Genetic epidemiology.** The branch of epidemiology dealing with biologically
3044 inherited causes of health and diseases. It is a bridging discipline between
3045 epidemiology and genetics, and it encompasses the study of the interactions between
3046 genes and environmental factors in disease causation.

3047

3048 **Harm.** An adverse consequence arising from a study, as opposed to a *benefit*. A
3049 potential harm is often referred to as a *risk*,” but that term is ambiguous because it
3050 encompasses both the magnitude and the probability of a harm occurring.

3051

3052 **Information.** Items of knowledge contained in materials, namely *records* (e.g., from
3053 hospitals, interviews, recorded measurements on people, etc.) or *biological samples*
3054 which can be tested in the laboratory for a variety of components. Records and
3055 biological samples may or may not be identified as belonging to a particular person

3056 and may or may not be linked to each other for the purpose of a study. The
3057 combinations of these different possibilities in various contexts (epidemiology,
3058 clinical trials, and genetic research) have been classified and labeled in different ways.
3059 In the present document, two major categories of information and materials have been
3060 utilized: *(personally) identifiable information*, which refer to, or can provide a link to,
3061 a particular person and *(personally) non-identifiable information*, which cannot be
3062 linked to a person. The two types of information respectively derive from *(personally)*
3063 *identifiable material* and *(personally) non-identifiable material* .

3064

3065 **Identifiable material.** This includes three types of materials:

- 3066 • *Nominal record or sample*: records and samples that carry the person's name
3067 or unique identifier, such as a social security number.
- 3068 • *Linked, coded record or biological sample*: a record or sample that does not
3069 carry a name but is coded and thus, by possessing or by "breaking" the coding
3070 system, could be linked to the person to whom the record refers or from whom
3071 the sample was obtained. Depending on the circumstances, the code may be
3072 known only to the person concerned or the key to the code may be held by the
3073 person who collected the material (such as the physician of the person
3074 concerned), by the repository where the record or sample is held, and/or by an
3075 investigator who is using the material in a study.
- 3076 • *Linked, double-coded record or sample*: similar to a *linked, coded record or*
3077 *biological sample* except that two different codes are used for each record or
3078 sample; one key, which connects the codes on different samples and records
3079 (and allows data derived from analysing samples to be compared to data from
3080 records), is created by the repository and used by investigators, while a
3081 separate coding system that links each record or sample to the person
3082 concerned is held by a third party (such as the physician who submitted the
3083 record or sample) and is not available to the investigator. Although double-
3084 coding makes linking samples or records to a particular person much more
3085 difficult, the existence of the codes means that such linkage might occur,
3086 either accidentally or through diligent effort.

3087

3088 **Intervention.** An intentional change induced by the investigator in the status of the
3089 study subjects in order to investigate its effects on health. Examples are the
3090 administration of a drug, vaccine, or health education programme. In contrast,
3091 procedures used to acquire data, such as administering a questionnaire, conducting an
3092 interview, taking a blood sample or performing an X-ray, are not regarded as
3093 “interventions” in the technical sense because they are not performed in order to
3094 produce a measurable effect on the subject.

3095

3096 **Interventional or intervention study.** An epidemiological study based on an
3097 *intervention*; synonymous with “experimental study”. Such studies test the effects of
3098 interventions (often termed “treatments” in the technical literature, not to signify that
3099 they are therapeutic but that they change the circumstances) which are assigned to
3100 subjects in a population following a study protocol. For example, an intervention
3101 would be a screening test for early recognition and management of a disease to be
3102 compared with no screening or with screening with lesser frequency; or a treatment
3103 could be a vaccine to prevent a disease of viral origin to be compared with no vaccine
3104 or a different vaccine. Whenever possible, subjects are assigned interventions at
3105 random (a *randomized controlled trial*). Random allocation means that, other than the
3106 intervention itself, all possibly relevant factors (both those already known to affect the
3107 outcomes being studied and those not yet identified) are on average equally
3108 distributed between groups receiving the different modalities; consequently, assuming
3109 the sample size is large enough to yield statistically significant results, random
3110 allocation ensures that any observed difference in outcomes can be confidently
3111 regarded as a real effect of the intervention.

3112

3113 **Investigation.** A study carried out for research purposes. It may also denote a study
3114 carried out for clinical diagnostic purposes and, sometimes, a specific diagnostic
3115 procedure (e.g., a breast echography, colonoscopy, or CT investigation).

3116

3117 **Linked, coded record or biological sample.** A type of *identifiable material*.

3118

3119 **Linked, double-coded record or biological sample.** A type of *identifiable material*.

3120

3121 **Minimal risk.** In this expression “risk” is taken in its common meaning of a possible
3122 but not certain adverse effect (on health). Minimizing risk implies reducing to the
3123 feasible minimum the number and magnitude of such possible effects as well as the
3124 probability that they will occur. A study is often said to involve “minimal risk” when
3125 the potential harms involved are comparable to those as experienced in “ordinary life”
3126 by a person of a given age and gender or by an apparently healthy person undergoing
3127 routine medical surveillance.

3128

3129 **Molecular epidemiology.** The use in epidemiological studies of techniques of
3130 molecular biology, better understood as a level and method of measurement rather
3131 than a branch of epidemiology with substantive research content.

3132

3133 **Nominal record or sample.** A type of *identifiable material*.

3134

3135 **Non-identifiable material.** Includes *unlinked records or biological samples* that were
3136 either collected on an *anonymous* basis or have been made anonymous (anonymized)
3137 in such a way that they do not carry any direct or indirect personal identifier . For
3138 these materials, no link is possible between the records or samples and the identity of
3139 the person who was the source of the record or sample.

3140

3141 **Observational study.** Synonymous of non-experimental study. An epidemiological
3142 study that does not involve an *intervention*. Observational studies have a wider range
3143 of applicability than *intervention studies* as they can be employed to investigate both
3144 putative hazardous or beneficial *factors* (e.g., in the environment, in diet), whereas,
3145 for obvious ethical reasons, intervention studies are typically limited to potentially
3146 beneficial factors. The results of observational studies, however, cannot usually be
3147 regarded with the same degree of confidence than the results from intervention
3148 studies. In observational studies the groups differently exposed to a *factor* (for
3149 example subjects with a high and low consumption of fats) may also differ in other
3150 factors, some of which are unknown and uncontrollable and may be the real cause of
3151 an observed effect (for example myocardial infarction). Therefore no single study can
3152 as a rule be regarded as providing firm evidence on the causal role, either hazardous
3153 or protective, of a factor. Multiple studies, carried out in different settings and

3154 producing consistent results, are necessary and should therefore not be considered as
3155 redundant or unethical.

3156

3157 **Placebo.** An inert medication or procedure given to “please” subjects so that they
3158 think they are receiving an active treatment for their condition. The effects, beneficial
3159 and sometimes even adverse, observed following the administration of a placebo are
3160 usually attributed to psychological processes (e.g., “the power of suggestion”).

3161

3162 **Publicly available record or information.** Any record or information, whether
3163 carrying personal identifiers or not, that the law treats as publicly accessible, such as a
3164 telephone directory, registry of deaths, or, in a number of countries, the register of
3165 nominal tax records. Since anyone can use these records, no special authorization or
3166 permission of any type - legal and/or ethical - is required for epidemiologists to
3167 consult them.

3168

3169 **Random allocation, random assignment or randomization.** Allocation of subjects
3170 to groups, for example to two pharmacological treatments, by a procedure that gives
3171 each subject the same probability of being assigned to either of the groups. Nowadays
3172 this is usually implemented by the use of a computer-generated sequence of random
3173 numbers; for example, each successive subject would assigned to one intervention if
3174 the corresponding random number is an even number and to the other if it is an odd
3175 number. Random allocation guarantees that all factors capable of influencing the
3176 study outcome (e.g., disease duration), other than the intervention being studied, are
3177 on average equally distributed between the two groups. Random allocation is the
3178 defining feature of a *randomized controlled trial*.

3179

3180 **Randomized controlled trial (RCT).** An *intervention study* involving *random*
3181 *allocation* of the subjects to different treatment modalities (*factors*); “randomized
3182 population trial” or “randomized prophylactic trial” are equivalent terms used for
3183 trials carried out to test a preventive measure in a healthy population.

3184

3185 **Random sampling.** A method of selecting units from a population in which each unit
3186 of the population has a known probability of selection. The unit can be the individual
3187 or, in *cluster sampling*, a group of individuals.

3188

3189 **Register and Registry.** A register is an ordered collection of records, for instance of
3190 births or of deaths. A registry is an organized system to develop, maintain and use one
3191 or more registers, for example a national registry may keep the registers of births and
3192 deaths. By extension the institution responsible for the system is also often called a
3193 registry (e.g., a cancer registry).

3194

3195 **Risk.** The probability that an event, favourable or adverse, will occur within a defined
3196 time interval. Although often contrasted to *benefit* (as in a “risk/benefit ratio”), the
3197 term “potential harm” is better for that context, leaving “risk” in its formal
3198 epidemiological sense to express the probability of a (typically adverse) event or
3199 outcome.

3200

3201 **Social epidemiology.** The branch of epidemiology dealing with socially relevant
3202 variables in relation to health. These variables characterize either the place of persons
3203 in society (e.g., gender, education, income, profession) or the structure and function of
3204 social institutions (e.g., family, school, government).

3205

3206 **Trial.** A generic term that in a clinical context denotes a research activity involving
3207 the administration of an intervention to humans to evaluate its safety and efficacy.

3208

3209 **Unlinked record or biological sample.** A *non-identifiable material*.

3210

3211 *Appendix 2.*

3212

3213 **Items to be included in a protocol (or associated documents) for**
3214 **epidemiological research involving human subjects**

3215

3216 This comprehensive checklist essentially reproduces Appendix 1 of the *International*
3217 *Ethical Guidelines for Biomedical Research Involving Human Subjects*. Since
3218 interventional epidemiological studies, such as a population-randomized controlled
3219 trial of a new vaccine, are similar to biomedical trials, this checklist is applicable;
3220 however, in observational studies, a number of items will not be relevant. In all cases
3221 it is up to the principal investigator to judge which items are pertinent - and to what
3222 extent - to a given study; likewise, the ethical review committee must be satisfied that
3223 the items included meet the requirements of the present Guidelines.

3224

3225 1. Title of the study;

3226

3227 2. A summary of the proposed research in lay/non-technical language;

3228

3229 3. A clear statement of the justification for the study, its significance in development
3230 and in meeting the needs of the country/population in which the research is carried
3231 out;

3232

3233 4. The investigators` views of the ethical issues and considerations raised by the
3234 study and, if appropriate, how it is proposed to deal with them;

3235

3236 5. Summary of published studies and of ongoing research pertinent to the topic,
3237 including relevant animal, preclinical and clinical studies;

3238

3239 6. A statement that the principles set out in these Guidelines will be implemented;

3240

3241 7. An account of previous submissions, if any, of the protocol for ethical review and
3242 their outcome;

3243

3244 8. A brief description of the site(s) where the research is to be conducted, including

3245 information about the adequacy of facilities for the safe and appropriate conduct
3246 of the research, and *relevant* demographic and epidemiological information about
3247 the country or region concerned;

3248

3249 9. Name and address of the sponsor;

3250

3251 10. Names, addresses, institutional affiliations, qualifications and experience of the
3252 principal investigator and other investigators;

3253

3254 11. The objectives of the study, its hypotheses or research questions, its assumptions,
3255 and its variables;

3256

3257 12. A detailed description of the design of the study, including whether it is an
3258 observational or interventional study, and if the latter, a description, among other
3259 things, of how subjects will be assigned to treatment groups (including the
3260 method of randomization, if used), and whether the study will be blinded (single
3261 blind, double blind) or open;

3262

3263 13. The number of research subjects needed to achieve the study objective, and how
3264 this was statistically determined;

3265

3266 14. The criteria for inclusion or exclusion of potential subjects, and justification for
3267 the exclusion of any groups on the basis of age, sex, social or economic factors, or
3268 for other reasons;

3269

3270 15. The justification for involving as research subjects any persons with limited
3271 capacity to consent or members of vulnerable social groups, and a description of
3272 special measures to minimize risks and discomfort to such subjects;

3273

3274 16. The process of recruitment, e.g., advertisements, and the steps to be taken to
3275 protect privacy and confidentiality during recruitment;

3276

3277 17. Description and explanation of any interventions (the method of treatment

3278 administration, including route of administration, dose, dose interval and
3279 treatment period for investigational and comparator products used);
3280
3281 18. When relevant, the plans and justification for withdrawing or withholding
3282 standard measures in the course of the research, including any resulting risks to
3283 subjects;
3284
3285 19. Any other treatment that may be given or permitted, or contraindicated, during
3286 the study;
3287
3288 20. Clinical and laboratory tests and other tests that are to be carried out on subjects
3289 or on biological samples obtained from the subjects;
3290
3291 21. The standardized case-report forms to be used, description and evaluation of the
3292 methods and frequency of measurement in gathering data from subjects,
3293 follow-up procedures, and, if applicable, the measures proposed to determine the
3294 extent to which subjects actually use or are exposed to the intervention;
3295
3296 22. Rules or criteria according to which subjects may be removed from the study or
3297 clinical trial, or, in a multi-centre study, a centre may be discontinued, or the
3298 study may be terminated;
3299
3300 23. Methods of recording and reporting adverse events or reactions, and provisions
3301 for dealing with complications;
3302
3303 24. The known or foreseen risks of adverse reactions, including the risks attached to
3304 each proposed intervention and to any drug, vaccine or procedure to be tested;
3305
3306 25. For research carrying more than minimal risk of physical injury, details of plans,
3307 including insurance coverage, to provide treatment for such injury, including the
3308 funding of treatment, and to provide compensation for research-related disability
3309 or death;
3310

- 3311 26. Provision for continuing access of subjects to the intervention after the study,
3312 indicating its modalities, the individual or organization responsible for providing
3313 it or paying for it, and for how long it will continue;
3314
- 3315 27. For research on pregnant women, a plan, if appropriate, for monitoring the
3316 outcome of the pregnancy with regard to both the health of the woman and the
3317 short-term and long-term health of the child;
3318
- 3319 28. The potential benefits of the research to subjects and to others;
3320
- 3321 29. The expected benefits of the research to the population, including new knowledge
3322 that the study might generate;
3323
- 3324 30. The means proposed to obtain individual informed consent and the procedure
3325 planned to communicate information to prospective subjects, including the name
3326 and position of the person responsible for obtaining consent;
3327
- 3328 31. When a prospective subject is not capable of informed consent, satisfactory
3329 assurance that permission will be obtained from a duly authorized person, or, in
3330 the case of a child who is sufficiently mature to understand the implications of
3331 informed consent but has not reached the legal age of consent, that knowing such
3332 child's agreement, or assent, will be obtained, as well as the permission of a
3333 parent or a legal guardian or other duly authorized representative;
3334
- 3335 32. An account of any economic inducements or other remuneration to prospective
3336 subjects for participation, and of any financial obligations assumed by the
3337 subjects, such as payment for medical services;
3338
- 3339 33. Plans and procedures, and the persons responsible, for communicating to subjects
3340 information arising from the study (on harm or benefit, for example), or from
3341 other research on the same topic, that could affect subjects' willingness to
3342 continue in the study;
3343

- 3344 34. Plans to inform subjects about the results of the study;
3345
- 3346 35. The provisions for protecting the confidentiality of personal data, and respecting
3347 the privacy of subjects, including the precautions that are in place to prevent
3348 disclosure of the results of a subject's genetic tests to immediate family relatives
3349 without the consent of the subject;
3350
- 3351 36. Information about how the code, if any, for the subjects' identity is established,
3352 where it will be kept and when, how and by whom it can be broken in the event
3353 of an emergency;
3354
- 3355 37. Any foreseen further uses of personal data or biological materials;
3356
- 3357 38. A description of the plans for statistical analysis of the study, including plans for
3358 interim analyses, if any, and criteria for prematurely terminating the study as a
3359 whole if necessary;
3360
- 3361 39. Plans for monitoring the continuing safety of drugs or other interventions
3362 administered for purposes of the study or trial and, if appropriate, the appointment
3363 for this purpose of an independent data-monitoring (data and safety monitoring)
3364 committee;
3365
- 3366 40. A list of the references cited in the protocol;
3367
- 3368 41. The source and amount of funding of the research: the organization that is
3369 sponsoring the research and a detailed account of the sponsor's financial
3370 commitments to the research institution, the investigators, the research subjects,
3371 and, when relevant, the community;
3372
- 3373 42. The arrangements for dealing with financial or other conflicts of interest that
3374 might affect the judgement of investigators or other research personnel: informing
3375 the institutional conflict-of-interest committee of such conflicts of interest; the
3376 communication by that committee of the pertinent details of the information to the

3377 ethical review committee; and the transmission by that committee to the research
3378 subjects of the parts of the information that it decides should be passed on to
3379 them;

3380

3381 43. The time schedule for completion of the study;

3382

3383 44. For research that is to be carried out in a developing country or community, any
3384 contribution that the sponsor will make to capacity-building for scientific and
3385 ethical review and for biomedical research in the host country, and an assurance
3386 that the capacity-building objectives are in keeping with the values and
3387 expectations of the subjects and their communities;

3388

3389 45. Particularly in the case of an industrial or commercial sponsor, a contract
3390 stipulating who possesses the right to publish the results of the study, and a
3391 mandatory obligation to prepare with, and submit to, the principal investigators
3392 the draft of the text reporting the results;

3393

3394 46. In the case of a negative outcome, an assurance that the results will be made
3395 available, as appropriate, through publication or, if relevant to the type of study,
3396 by reporting to the drug registration authority;

3397

3398 47. Circumstances in which it might be considered inappropriate to publish findings,
3399 such as when the findings of an epidemiological, sociological or genetics study
3400 may present risks to the interests of a community or population or of a racially or
3401 ethnically defined group of people, and the procedures by which such a
3402 determination would be made; and

3403

3404 48. A statement that any proven evidence of falsification of data will be dealt with in
3405 accordance with the policy of the sponsor or of the legal authorities to take
3406 appropriate action against such unacceptable procedures.

3407

3408 *Appendix 3.*

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3416

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse

consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially

important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (See footnote)
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. (See footnote)
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

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3419 *Appendix 4.*

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3421 **Members of the CIOMS/WHO Core Group established**
3422 **to carry out drafting of the provisional text of Guidelines**

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