

COMPARISON OF INTERNATIONAL GUIDELINES FOR RESEARCH INVOLVING HUMANS

Regulation, Guideline, Instrument, or Directive	TOPIC ¹						
	Independent Review (by IRB and/or Ethics Committee)	Favorable risk-benefit ratio, scientific validity, and social value	Informed consent, including special populations	Justice and the fair selection of study population; respect for recruited participants and study communities	Data and safety monitoring/ Quality assurance and quality control	Standard of care for control groups; provision of new product or best treatment upon conclusion of the study	Other (including requirements regarding trial registration, control group treatment, privacy, etc.)
Opinion of European Group on Ethics in Science and New Technologies to the European Commission on Ethical Aspects of Clinical Research in Developing Countries (Feb. 2003)	<ul style="list-style-type: none"> ▪ Ethics committees from all countries involved should conduct scientific and ethical evaluation of the protocol (2.8) ▪ Host countries should have an appropriate legal and ethical framework to carry out evaluation effectively and independently (2.8) ▪ If they exist, local ethics committees in host countries should be involved (2.8) ▪ If no local representative can be involved, then clinical trial should not be implemented in host country (2.8) ▪ Use of placebo must be justified in protocol and approved by committee (2.10) 	<ul style="list-style-type: none"> ▪ Principles of beneficence and non-maleficence should be respected (2.2) ▪ Should consider risk/benefit ratio at both individual and community level (2.9) ▪ Should consider impact of trial on local community (2.9) ▪ Research should be relevant to host country (2.9) 	<ul style="list-style-type: none"> ▪ Participation should not be induced by financial or other undue inducement (1.32) ▪ Should respect individual autonomy by seeking informed consent of participants (2.2) ▪ Should respect local conditions and traditions (2.7) ▪ Should seek agreement from community representative or family when appropriate, but free consent always has to be given by each participant capable of decision making (2.7) 	<ul style="list-style-type: none"> ▪ Principles of respect for human dignity, non-exploitation, non-discrimination, and non-instrumentalization apply in developing countries as in industrialized countries (2.2) ▪ Principle of justice should be applied; burdens of research should fall on those most likely to benefit (2.2) ▪ Should include local scientists in early planning stages and use their knowledge of local conditions and traditions to identify local needs (2.4) ▪ Trials should not be carried out in countries with less adequate healthcare unless specific justification can be given, such as that the trial addresses a specific health condition of the country (2.5) 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ A sponsor's responsibility towards patients and local community does not end with the end of the clinical trial (1.33) ▪ Use of placebo should be subject to same principles as in European countries, except use of best proven treatment may not be required where it is not locally available (2.10) ▪ Sponsor should provide standard treatment if country or community health services cannot do so due to cost (2.12) ▪ Proven beneficial drug should be supplied to all participants when trial ends, even if this means supplying drug for a lifetime (2.13) ▪ Trial should also benefit community that contributed to the drug's development, either through provision of an affordable supply of the drug or through capacity building (2.13) ▪ Protocol should specify 	<ul style="list-style-type: none"> ▪ Should respect individual autonomy by respecting privacy and confidentiality of personal data (2.2) ▪ Researchers have a moral duty to make concrete contributions to improve standards of living and access to healthcare (2.3) ▪ Values and ethical principles of sponsors and host country should be considered and compromises negotiated while respecting fundamental human rights standards (2.6) ▪ Need transparency in terms of financing of research (2.9) ▪ Liability and indemnity insurance should be provided to participants (2.11) ▪ Results should be regarded as falling within public domain or should consider a system of compulsory licenses for applications in developing countries (2.13)

¹ To convey accurately important provisions, this summary chart both paraphrases and liberally uses language from the original documents. Quotation marks are omitted for ease of reading, but specific references are included.

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<i>Opinion of European Group (cont.)</i>						who will benefit from the trial, how and for what period of time (2.13)	<ul style="list-style-type: none"> ▪ Scientists, doctors, and participants should be informed of results, even if negative (2.14) ▪ Results must be made accessible to scientific community and general population of host country (2.14) ▪ Local scientists and clinicians should be recognized adequately in both publications and patents (2.14)
Nuffield Council on Bioethics Report (April 2002)	<ul style="list-style-type: none"> ▪ Recommends all countries establish a system for ethical review of research, including independent research ethics committees (10.38) ▪ Research should be reviewed in both the host and sponsor countries (10.40) ▪ Sponsors should ensure adequate ethics training of all research professionals (10.18) 	<ul style="list-style-type: none"> ▪ N/A (refers to other guidance, such as the Declaration of Helsinki) 	<ul style="list-style-type: none"> ▪ In some contexts may need to obtain agreement from community or assent from a senior family member prior to approaching prospective participants (10.22) ▪ Genuine consent to participate must be obtained from each participant (10.19) ▪ Level of inducement must be appropriate (10.23) ▪ If inappropriate for consent to be recorded in writing, oral consent must be obtained (10.25) 	<ul style="list-style-type: none"> ▪ Researchers have a duty to alleviate suffering, show respect for persons, be sensitive to cultural differences, and not exploit the vulnerable (4.6; 10.2) ▪ Unacceptable to select populations that are economically or politically weak and therefore vulnerable to exploitation in order to test therapies more cheaply or in order to use the results for the benefit of other, more wealthy, communities (10.16) 	<ul style="list-style-type: none"> ▪ Before research is undertaken, should address the need to monitor for long-term deleterious outcomes for a period of time after the completion of the study (10.48) 	<ul style="list-style-type: none"> ▪ Wherever appropriate, participants in control group should be offered best current method of treatment available anywhere in the world (universal standard of care) or at least best intervention currently available as part of the national public health system (10.30) ▪ Must decide before research begins whether, when research ends, control group will be offered intervention shown to be more effective (10.33, 10.45) ▪ Should try to secure post-trial access to effective interventions for all trial participants that could 	<ul style="list-style-type: none"> ▪ External sponsors have an obligation to train host country in methods and skills of conducting research (10.5) ▪ All countries should set priorities for research into healthcare (10.9) ▪ When external sponsors propose research that falls outside the host country's national priorities should be required to justify the topic to the appropriate research ethics committees (10.10)

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<i>Nuffield Report (cont.)</i>						<ul style="list-style-type: none"> benefit (10.46) <ul style="list-style-type: none"> ▪ Should consider possibility of introducing and maintaining successful treatment in wider community before commencing research (10.47) ▪ Participants in preventive measure research who develop the disease being studied should receive the universal standard of care or the best available intervention (10.34) 	
CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (revised 2002)	<ul style="list-style-type: none"> ▪ Research must undergo independent scientific and ethics review (Guideline 2) ▪ May use investigational therapy compassionately without prior review if: (1) patient needs emergency treatment; (2) there is evidence that treatment may be effective; and (3) there is no alternative treatment that is as good or better; in such cases need to report to ethics review committee within one week (Commentary on Guideline 2) ▪ Review committee may be created at national, regional or local level, and membership should 	<ul style="list-style-type: none"> ▪ Research must be scientifically valid (Guideline 1) ▪ Research must have prospect of improving health (Guideline 1) ▪ Investigator must ensure that benefits and risks are reasonably balanced and risks are minimized (Guideline 8) 	<ul style="list-style-type: none"> ▪ Must obtain voluntary informed consent of all participants or their authorized representative (Guideline 4) ▪ Waiver of informed consent should be uncommon and exceptional and must be approved by the ethics review committee (Guideline 4) ▪ Information must be conveyed in suitable language (Commentary to Guideline 4) ▪ Investigator must ensure comprehension of information (Commentary to Guideline 4) ▪ Signed consent forms should be used unless 	<ul style="list-style-type: none"> ▪ Researchers and investigators must make every effort to ensure that research in a population or community with limited resources is responsive to the needs and priorities of the population or community (Guideline 10) ▪ Groups or communities should be selected so that burdens and benefits are equitably distributed (Guideline 12) ▪ Must justify exclusion of groups or communities that might benefit from study participation (Guideline 12) ▪ Special justification is required to include vulnerable individuals 	<ul style="list-style-type: none"> ▪ Independent review committees should conduct periodic reviews (Guideline 2) ▪ Protocol must provide for monitoring of data by an independent Data and Safety Monitoring Board if trial is designed to prevent or postpone a lethal or disabling outcome (Commentary to Guideline 8) ▪ Normally, establish criteria for premature termination at outset of randomized controlled trial (Commentary to Guideline 11) ▪ In most cases, unnecessary to appoint DSMB—an individual can 	<ul style="list-style-type: none"> ▪ Researchers and investigators must make every effort to ensure that any intervention or product developed, or knowledge generated, through research in a population or community with limited resources is made reasonably available for the population's or community's benefit (Guideline 10) ▪ Control group may be given an established effective intervention rather than best available treatment (Guideline 11) ▪ Placebo may be used if there is no established effective intervention, if 	<ul style="list-style-type: none"> ▪ Multi-center trials need to be carried out in uniform fashion, following same protocol or making necessary provisions to ensure data validity (Commentary on Guideline 2) ▪ Investigators should have access to data and be able to analyze if and publish manuscripts freely (Commentary on Guideline 2) ▪ Investigator must safeguard confidentiality of research data and should inform subject of confidentiality policy (Guideline 18) ▪ Injured subjects should be ensured access to free

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CIOMS Guidelines for Biomedical Research (cont.)	<p>include physicians, scientists, other professionals and lay persons representing community (Commentary on Guideline 2)</p> <ul style="list-style-type: none"> ▪ Must disclose potential or apparent conflict of interests to ethics review committee (Commentary on Guidelines 2 & 3) ▪ Protocol should be reviewed in sponsor's home country, but need to take into account the host country in reviewing the study (Guideline 3) 		<p>ethics review committee waives the requirement because research involves only minimal risk or if such forms would be an unjustified threat to subject's confidentiality (Commentary to Guideline 4)</p> <ul style="list-style-type: none"> ▪ Consent requirement may be waived if it would make research impracticable (Commentary to Guideline 4) ▪ Must respect community culture and customs (Commentary to Guideline 4) ▪ Use of medical records and biological specimens may require additional consent, and is subject to certain constraints (Commentary to Guideline 4) ▪ Subject must be provided with specific information (see Guideline 5) ▪ Sponsors and investigators have specific duties regarding informed consent (Guideline 6) ▪ May reimburse, provide free medical services to, or pay subjects, if approved by ethics review committee and not undue inducement (Guideline 7) 	<p>(Guideline 13)</p> <ul style="list-style-type: none"> ▪ Where vulnerable individuals are selected to participate in a study, the means of protecting their rights and welfare must be strictly applied (Guideline 13) ▪ Research involving children must meet certain criteria (Guideline 14) ▪ Research involving individuals who by reason of mental or behavioral disorders are not capable of giving adequately informed consent must meet certain criteria (Guideline 15) ▪ Women of reproductive age should not be excluded from research, but risks must be thoroughly discussed (Guideline 16) ▪ Access to pregnancy test and contraceptives should be guaranteed if research possibly hazardous to fetus or woman if she becomes pregnant (Guideline 16) ▪ Pregnant women should be presumed eligible, but should only be included in research in certain situations (Guideline 17) 	<p>be appointed to advise on need to consider changing the system of monitoring for adverse events or process of informed consent, or to consider terminating study (Commentary to Guideline 11)</p>	<p>withholding the established effective intervention would cause no more than temporary discomfort or delay in relief of symptoms, or if necessary to obtain scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to subjects (Guideline 11)</p> <ul style="list-style-type: none"> ▪ Where established effective intervention is not available to the study population, there must be an assurance that, if the investigational intervention proves to be safe and effective, it will be made reasonably available to the study population (Commentary to Guideline 11) 	<p>medical treatment and compensation (Guideline 19)</p> <ul style="list-style-type: none"> ▪ In case of death, dependents of subject are entitled to compensation (Guideline 19) ▪ In externally collaborative research, sponsors and investigators have an ethical obligation to ensure that the projects contribute to capacity-building in the host country (Guideline 20)

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<i>CIOMS Guidelines for Biomedical Research (cont.)</i>			<ul style="list-style-type: none"> ▪ For groups incapable of giving informed consent, risk from non-beneficial interventions should be no more likely and not greater than the risk of routine medical or psychological examination (or slightly higher risk if there is an overriding scientific or medical rationale and an ethics review committee has approved the research) (Guideline 9) ▪ Research involving individuals who by reason of mental or behavioral disorders are not capable of giving adequately informed consent must meet certain criteria (Guideline 15) 	<ul style="list-style-type: none"> ▪ IRC should determine whether research objectives are responsive to community needs (Commentary on Guideline 3) ▪ Need to respect community customs and traditions (Commentary on Guideline 3) 			
U.S. National Bioethics Advisory Commission, Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (April 2001)	<ul style="list-style-type: none"> ▪ Ethics review committee must review research (Rec. 1.1) ▪ Researchers should justify the study design, including procedures for minimizing risks and level of care provided to the control group, to the ethics review committee (Recs. 2.1 & 2.2) ▪ Representatives of host country should be involved in reviewing trials 	<ul style="list-style-type: none"> ▪ Risk to participants must be minimized and must be reasonable in relation to potential benefits (Rec. 1.1) 	<ul style="list-style-type: none"> ▪ Must obtain informed consent from competent adult participants (Recs. 1.1; 3.1) ▪ Information should be disclosed in a culturally appropriate, understandable way developed through consultation with community representatives (Recs. 3.2 & 3.5) ▪ Researchers should seek 	<ul style="list-style-type: none"> ▪ All participants must be treated with equal regard (Rec. 1.1) ▪ Burdens and benefits of research must be equitably distributed (Rec. 1.1) ▪ Trials in developing countries should be responsive to the needs of the host country (Rec. 1.3) ▪ Community representatives should be 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ Control group should receive established effective treatment, whether or not the treatment is available in the host country (Rec. 2.2) ▪ Researchers and sponsors should make reasonable, good faith efforts to ensure continued access by participants to experimental interventions 	<ul style="list-style-type: none"> ▪ Research must, at a minimum, comply with the ethical principles of the Belmont Report (p. ii) ▪ Researchers must provide adequate care and compensation for research-related injuries (Rec. 1.1) ▪ Where applicable, U.S. sponsors and researchers should assist developing countries in building their capacity for designing,

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<p><i>U.S. National Bioethics Advisory Commission, Developing Countries (cont.)</i></p>	<p>(p. iv)</p> <ul style="list-style-type: none"> ▪ Protocol should describe how community will be involved in trial design and implementation or justify why such involvement is impossible or irrelevant (Rec. 2.3) ▪ Protocol should justify the plans for information disclosure for informed consent purposes, and should ensure information is provided to participants in an understandable manner (Recs. 3.2; 3.4) ▪ Ethics review committees should require that information about any post-trial benefits be provided during the informed consent process (Rec. 3.3) ▪ Protocol should indicate how researchers will inform participants that the purpose of the trial is to contribute to scientific knowledge rather than solely to administer treatment (Rec. 3.10) ▪ Ethics review committees should be allowed to waive requirement for written and signed consent, provided that the protocol specifies how consent can be verified 		<p>permission of community representatives where necessary, but such permission may not be substituted for a competent individual's voluntary informed consent (Rec. 3.6)</p> <ul style="list-style-type: none"> ▪ Researchers should allow a participant to involve family member in the consent process, but a family member's permission may not be substituted for a competent individual's voluntary informed consent (Rec. 3.8) ▪ The consent process should be the same for men and women, and, although the permission of a man for a woman's participation may be necessary and permissible under certain circumstances, another person's consent may not be substituted for that of a competent adult woman's individual consent (Rec. 3.9) ▪ Ethics review committees should be allowed to waive requirement for written and signed consent, provided that the protocol specifies how 	<p>involved in design and implementation of research projects (Rec. 2.3)</p>		<p>that have been proven effective; if no such arrangements are planned, should justify to ethics review committee (Rec. 4.1)</p> <ul style="list-style-type: none"> ▪ Research proposals should explain how new effective interventions will become available to some or all of the host country's population, or explain why, absent such a plan, the research nonetheless responds to the country's health needs (Rec. 4.2) ▪ When possible, agreements should be negotiated, prior to the beginning of a trial, to make effective interventions or other research benefits available to the host country after the study's completion (Rec. 4.3) 	<p>reviewing, and conducting clinical trials (Rec. 5.6)</p> <ul style="list-style-type: none"> ▪ Where applicable, U.S. sponsors and researchers should assist developing countries in establishing and building the capacity of ethics review committees (Rec. 5.7)

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<i>U.S. NBAC, Developing Countries (cont.)</i>	(Rec. 3.11) <ul style="list-style-type: none"> ▪ Trials should be reviewed by both a U.S. IRB and an ethics review committee in the host country unless the U.S. government has found the host country's or the host institution's human participant's protection system provide sufficient ethical protections (Rec. 5.2) 		<ul style="list-style-type: none"> consent can be verified (Rec. 3.11) ▪ Research should be conducted regarding the informed consent process in various cultural settings and international educational efforts undertaken to share knowledge about the process (3.12) 				
Directive 2001/20/EC (good clinical practice in the conduct of clinical trials on medicinal products for human use) (2001)	<ul style="list-style-type: none"> ▪ Ethics committee must continually monitor and weigh benefits and risks (Art. 3.2(a)) ▪ A sponsor may not start a clinical trial without the favorable opinion of the relevant Ethics Committees and competent authority of the relevant Member State (Art. 9.1) ▪ Certain amendments to the conduct of a clinical trial may be made after the trial begins (Art. 10) 	<ul style="list-style-type: none"> ▪ Benefits must justify risks, as determined by the Ethics Committee (Art. 3.2(a)) 	<ul style="list-style-type: none"> ▪ Persons incapable of giving legal consent should receive special protection and should not be subjects unless the study would directly benefit the patient and outweigh risks (3 & 4) ▪ Some clinical trials should involve children, but special provisions apply to clinical trials on minors (3 & Art. 4) ▪ Must be written, dated, and signed by subject or legal representative (except if person concerned is unable to write, in which case oral consent may be acceptable, depending on national laws) (Art. 2(j); 3.2(d)) ▪ Subjects may withdraw at any time by revoking 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ Member State inspectors will verify compliance with standards of good clinical practice and inspect data (15; Art. 15) ▪ Adverse reactions must be monitored to immediately terminate any trial involving unacceptable risk (18; Art. 16) ▪ Investigators shall report all serious adverse events immediately to the sponsor unless protocol requires otherwise; sponsor shall report such events to competent authorities and the Ethics committee (Art. 16.1; Art. 17) 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ The directive implements good clinical practice and does not apply to non-interventional trials (Art. 1) ▪ Relevant Member States must enter certain information in the European clinical trials database (Art. 11) ▪ The principles of good manufacturing practice should apply to investigational medicinal products (12) ▪ Special provisions should apply to non-commercial clinical trials conducted without the participation of the pharmaceuticals industry (14) ▪ Personal information of subjects must be treated as confidential, but subject to inspection by authorized persons (16)

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<i>EC Directive 2001/20/EC (cont.)</i>			informed consent (Art. 3.2(e)) <ul style="list-style-type: none"> Special provisions apply to trials on incapacitated adults (Art. 5) 				<ul style="list-style-type: none"> Preempts any less comprehensive national provisions for the protection of human subjects (Art. 3) Must safeguard integrity and privacy of subjects (Art. 3.2(c)) Must make provisions for insurance or indemnity to cover liability of investigator and sponsor (Art. 3.2(f)) Member states may suspend trials under certain circumstances (Art. 12) An authorization is required for the manufacture and import of investigational medicinal products, and there must be at least one qualified person responsible for ensuring compliance with requirements (Art. 13) Certain requirements apply to the labeling of investigational medicinal products (Art. 14) Sponsor or sponsor's legal representative must be established in the EU (Art. 19)
UNAIDS Guidance: Ethical Considerations in	<ul style="list-style-type: none"> HIV vaccine trials should be reviewed by scientific and ethics review 	<ul style="list-style-type: none"> HIV vaccine research should be scientifically valid (G.P. 4) 	<ul style="list-style-type: none"> The research protocol should describe the social context of proposed study 	<ul style="list-style-type: none"> Proposed HIV vaccine research should potentially benefit the 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Any safe and effective vaccine, knowledge, or benefits resulting from 	<ul style="list-style-type: none"> The early ethical development of effective HIV vaccines should be

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<p>HIV Preventive Vaccine Research (2000, reprint 2004)</p> <p><i>UNAIDS Guidance (cont.)</i></p>	<p>committees located in, and including members from, the host country and community (G.P. 6)</p>	<ul style="list-style-type: none"> ▪ In general, early phases of clinical trials should be conducted among less vulnerable communities, usually within the host country, unless valid scientific reasons exist for and proper ethical safeguards are taken in conducting the research on another population (G.P. 8) 	<p>population and the potential for exploitation or increased vulnerability among participants (G.P. 7)</p> <ul style="list-style-type: none"> ▪ Risks of HIV vaccine trial should be specified in research protocol (G.P. 9) ▪ Potential benefits should be included in the protocol, but not in a way that unduly influences participation (G.P. 10) ▪ Independent informed consent should be solicited from subjects at various stages, including prior to enrollment in a trial (G.P. 12) ▪ Information should be provided in a culturally appropriate way (G.P. 12) ▪ During the trial, efforts should be made to ensure that participants continue to understand and participate freely (G.P. 12) ▪ Pre- and post-test counseling should be provided for any HIV testing before, during, and after research (G.P. 12) ▪ Third-party authorization should be obtained from the community where necessary, but cannot substitute for individual informed consent, except 	<p>population from which subjects are recruited (G.P. 4)</p> <ul style="list-style-type: none"> ▪ Study community representatives should be involved in the design, implementation, and dissemination of results of HIV vaccine research (G.P. 5) ▪ Protocol should include steps for protecting the dignity, safety, and welfare of study subjects (G.P. 7) ▪ Women and children should be included in clinical trials for HIV vaccines (G.P. 17 & 18) 		<p>HIV vaccine research should be made available to trial participants and high risk populations (G.P. 2)</p> <ul style="list-style-type: none"> ▪ A placebo control arm is ethically acceptable in a phase III HIV vaccine trial as long as there is no known effective HIV vaccine, but a vaccine against another disease should be considered for use as placebo (e.g. hepatitis B or tetanus) (G.P. 11) ▪ The best proven or, at a minimum, the community standard care and treatment for HIV/AIDS should be provided to participants, according to a plan developed prior to the commencement of the trial (G.P. 16) 	<ul style="list-style-type: none"> ▪ promoted (G.P. 1) ▪ Capacity building in host countries should be pursued (G.P. 3) ▪ Should provide highest level of care for adverse reactions, compensation for injury, and referral to psychosocial and legal support, if necessary (G.P. 9) ▪ The latest risk-reduction counseling and prevention methods should be provided to all participants (G.P. 14) ▪ Before the trial begins, a plan for monitoring the informed consent process and risk-reduction interventions should be established and approved by the IRB (G.P. 15)

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<i>UNAIDS Guidance (cont.)</i>			<p>in the case of certain minors (G.P. 12)</p> <ul style="list-style-type: none"> ▪ Measures should be taken to protect vulnerable populations, such as junior or subordinate individuals, persons engaged in illegal or stigmatized activities, women, and low income individuals (G.P. 13) ▪ Women should be provided with adequate information about risks to themselves, their fetus, or breast-fed infants to allow them to make adequately informed choices about participation (G.P. 17) 				
WHO Operational Guidelines for Ethics Committees that Review Biomedical Research (2000)	<ul style="list-style-type: none"> ▪ Ethics committees (ECs) safeguard the dignity, rights, safety and well-being of actual or potential subjects (2) ▪ ECs should review proposed studies independently and efficiently before research begins and on an ongoing basis (2) ▪ Countries should establish ethics review systems and promote establishment of ECs (3) ▪ ECs should be multidisciplinary, and should be established 	<ul style="list-style-type: none"> ▪ ECs should consider the scientific validity of the study design (6.2.1) ▪ Follow-up review may be required if an event or new information affects the benefit/risk ratio of a study (9) 	<ul style="list-style-type: none"> ▪ The EC should ensure that adequate information is provided in an understandable way to subjects and/or their legal representatives in order to obtain informed consent (6.2.4) ▪ The influence of the community on informed consent of individuals should be taken into account (6.2.6) 	<ul style="list-style-type: none"> ▪ The principles of respect and justice govern ethics committees, and the benefits and burdens of research must be fairly distributed (2) ▪ EC review should consider the impact on the community (6.2.6) 	<ul style="list-style-type: none"> ▪ Serious adverse events may require follow-up review of a study (9) 	<ul style="list-style-type: none"> ▪ EC should consider how research results will be made available to subjects and study communities (6.2.6) 	<ul style="list-style-type: none"> ▪ Research participants' confidentiality should be protected (6.2.4) ▪ Among factors to be considered in EC review are insurance and indemnity arrangements, and provisions for compensation or treatment in the event of injury, disability or death of a subject (6.2.3)

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	according to applicable laws and regulations and community values (4) <ul style="list-style-type: none"> ▪ ECs should establish and follow publicly available standard operating procedures and an application procedure for research review (5) 						
European Medicines Agency—ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) (1997)	<ul style="list-style-type: none"> ▪ Trials should be conducted in accordance with IRB-approved protocols that include appropriate topics (§2.6; §6) ▪ Should review ongoing trials at least once per year (§3.1.4) ▪ Should document and follow written procedures in accordance with §3.3 ▪ Should retain all relevant records (§3.4) ▪ Should approve written consent form (§4.8.1) 	<ul style="list-style-type: none"> ▪ A trial should be initiated only if the anticipated benefits justify the risks (§2.2) ▪ Trials should be scientifically sound (§2.5) 	<ul style="list-style-type: none"> ▪ Written informed consent should be provided by each participant (§2.9) ▪ Subjects should not be coerced or unduly influenced to participate (§4.8.3) ▪ The subject should be informed of pertinent aspects of the trial, as noted in §4.8.10, in understandable language (§§4.8.5-4.8.6) ▪ In the case of individuals unable to consent due to incapacity, a legal representative may consent to participation (§§4.8.12) ▪ In the case of trials with no anticipated direct clinical benefit for the subject can only be conducted with subjects who personally consent, unless certain criteria apply (§4.8.14) 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ The sponsor should implement quality assurance and quality control systems and procedures (§2.13; §5.1) ▪ Serious adverse events should be reported immediately to the sponsor unless the protocol specifies otherwise (§4.11.1) ▪ Even where the sponsor transfers trial-related duties and functions to a contract research organization, the sponsor has the ultimate responsibility for the quality and integrity of the trial data (§5.2.1) ▪ Sponsor may consider establishing a data-monitoring committee to assess the trial according to written operating procedures, and may recommend to the sponsor whether to 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ Confidentiality of records should be protected (§2.11) ▪ Several provisions relating to investigators (§4) ▪ Sponsor should ensure that investigational product is manufactured in accordance with applicable GMP and comply with other provisions regarding investigational product (§5.13-5.14, §5.16) ▪ Trials should be properly monitored (§5.18) ▪ Special provisions for multi-center trials (§5.23) ▪ An investigator's brochure should include information outlined in §7 ▪ Essential documents identified in §8 should be generated and on file prior to the start of the trial

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					continue, modify or stop a trial (§5.2.2) <ul style="list-style-type: none"> ▪ Should expedite Adverse drug reporting (§5.17.1) ▪ Quality assurance audits should comply with applicable provisions (§5.19) 		
Council of Europe, Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (1997)	<ul style="list-style-type: none"> ▪ Research must be approved by an independent body after scientific and ethics review (Art. 16) 	<ul style="list-style-type: none"> ▪ Research must not involve risks that are disproportionate to the potential benefits (Art. 16) 	<ul style="list-style-type: none"> ▪ Subjects must give free and informed consent on the basis of appropriate information regarding the purpose and nature of the study (Art. 5 & 17) ▪ A person lacking the capacity to consent should not be a research subject unless the study is directly for his or her benefit (Art. 6 & 17) ▪ In the case of incapacitated individuals, such as minors, the authorization of a legal representative is required and the individual's opinion should be considered to the extent possible (Art. 6 & 17) ▪ Informed consent or authorization by a legal representative may be withdrawn at any time (Art. 5, 6 & 17) ▪ An incapacitated person may be a research subject if certain 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ The privacy of health information should be respected (Art. 10) ▪ Research on embryos in vitro shall ensure adequate protection for the embryos (Art. 18) ▪ Embryos may not be created for research purposes (Art. 18) ▪ A person who is injured or damaged by an intervention should receive fair compensation as prescribed by law (Art. 24)

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			conditions are met, including that the research involves a minimal risk and burden on the individual (Art. 17)				
WHO Guidelines for Good Clinical Practice for trials on pharmaceutical products (1995)	<ul style="list-style-type: none"> ▪ Written protocol, signed by the investigator and sponsor, should be reviewed from a scientific and ethical standpoint by independent review bodies (2) ▪ The protocol should include specific items (2; Appendix 2) ▪ The ethics committee should ensure the protection of the rights and welfare of subjects (3.2) ▪ Ethics committee should be independent and should have documented, publicly available policies and procedures (3.2) ▪ Ethics committee has ongoing responsibility for conduct of trial, and should be informed of amendments to the protocol, serious adverse events, or other pertinent safety-related information 	<ul style="list-style-type: none"> ▪ Risks and benefits must be considered and the trial must be scientifically valid and ethically justified (1.1) ▪ Pharmaceutical, pre-clinical, and clinical data must be adequate to support the phase of the trial (1.3) 	<ul style="list-style-type: none"> ▪ The informed consent principles from the Declaration of Helsinki and the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects should be implemented (3.3) ▪ Information should be provided in an understandable form and potential subjects must be allowed to ask questions (3.3) ▪ Consent should be properly recorded (3.3.d) ▪ Careful consideration should be given when obtaining consent from members of a hierarchical group to ensure voluntary participation (3.3e) ▪ Subjects incapable of consenting may participate provided the law, ethics committee, and the subject's legal 	<ul style="list-style-type: none"> ▪ Ethical principles of justice and respect for persons must be followed (1.2) 	<ul style="list-style-type: none"> ▪ Sponsor must appoint qualified monitors and establish a system of quality assurance (including independent auditing) (5.10, 5.11, & 12) ▪ The monitor has certain responsibilities, including ensuring proper data handling and reporting, assessing the trial site, educating staff, overseeing completion of case-report forms, etc. (6) ▪ The monitor should follow predetermined written standard operating procedures (6) ▪ Adverse events must be monitored carefully and recorded in detail, according to the trial protocol (7.1) ▪ Sponsors should consider establishing a special committee to monitor adverse events (7.1) 	<ul style="list-style-type: none"> ▪ Investigator should provide relevant follow-up procedures for an appropriate period of time after trial (4.1) ▪ Investigator should provide adequate and safe medical or dental care for subjects during trial (4.1) 	<ul style="list-style-type: none"> ▪ Sponsor and investigator(s) should agree on responsibility for regulatory compliance prior to start of trial (1.5) ▪ All parties involved in research should comply with existing national regulations and requirements, or, in their absence, the designated guidelines (1.5) ▪ The Declaration of Helsinki is the standard basis for ethics (2.1) ▪ Confidentiality should be protected (3.3b; 3.4) ▪ Subject should have access to insurance, compensation, and treatment information should he or she be injured or disabled in the trial (3.3c) ▪ The investigator has certain other responsibilities, including selecting subjects,

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WHO Guidelines on GCP (cont.)	(3.2)		representative allow the participation (3.3f) <ul style="list-style-type: none"> ▪ Personal, written consent is required for non-therapeutic studies (3.3g) 		<ul style="list-style-type: none"> ▪ Adverse event reporting, by both the investigator and the sponsor, should be according to the protocol and the applicable national regulations, which typically require accelerated reporting of serious events (7.2) ▪ Data management should be documented and responsibilities should be allocated according to the guidelines, protocol, or by written agreement between investigator and sponsor (8) 		ensuring compliance with the protocol, providing information for informed consent, selecting the site and staff, obtaining ethical review, etc. (4) <ul style="list-style-type: none"> ▪ The sponsor has certain responsibilities, including selecting the investigator, delegating responsibilities to the investigator or a contract research organization, supplying the investigational product, establishing written standard operating procedures to comply with Good Clinical Practice, etc. (5) ▪ Sponsor should have a local representative to fulfill responsibilities governed by national regulations (5) ▪ Sponsor is ultimately responsible for ensuring compliance with applicable legal, ethical, and regulatory requirements and for providing compensation and indemnity for trial-related injury or death (5) ▪ Special requirements apply regarding statistics and calculations, including randomization and blinding (9)

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WHO Guidelines on GCP (cont.)							<ul style="list-style-type: none"> ▪ The sponsor, investigator, and monitor have certain responsibilities with regard to the handling of and accountability for pharmaceutical products, including supply, storage, labeling, and packaging (10) ▪ The role of the national drug regulatory authority should include oversight of protocols, among other responsibilities (11) ▪ For multi-center trials, a special administrative system, including committees for particular functions described in the protocol, may be necessary (13; Appendix 3)
CIOMS International Guidelines for Ethical Review of Epidemiological Studies (1991)	<ul style="list-style-type: none"> ▪ Epidemiological studies should be reviewed independently on ethical grounds, except if the study is an investigation of an outbreak of acute communicable disease (Ethical Review Procedures) ▪ Ethics review committees should establish working rules (Ethical Review Procedures) ▪ Ethics review process should include 	<ul style="list-style-type: none"> ▪ Must maximize possible benefits while minimizing possible harm, and research must be reasonable in light of expected benefits (General Ethical Principles; Minimizing Harm) ▪ Research design must be sound (General Ethical Principles) ▪ Investigators must be competent to conduct the research and to assure 	<ul style="list-style-type: none"> ▪ Informed consent usually should be sought from participants in epidemiological studies (Informed Consent) ▪ Ethics review committee must approve any waiver of informed consent, such as when impractical to obtain, counterproductive to study purpose, or because subjects are aware through public announcements that personal data are 	<ul style="list-style-type: none"> ▪ Must respect the autonomy of those who are capable of deliberation about their personal goals (General Ethical Principles) ▪ Must protect those with impaired or diminished autonomy against harm and abuse (General Ethical Principles) ▪ Class of persons bearing the burden of research should receive an appropriate benefit 	<ul style="list-style-type: none"> ▪ Data must be presented honestly and objectively (Conflict of Interest) ▪ Studies will be terminated prematurely if the outcome in one group is clearly superior to the outcome in the other, and all subjects will be offered the superior treatment (Ethical Review Procedures) ▪ Research protocols should include rules regarding when a study 	<ul style="list-style-type: none"> ▪ Control groups should receive the most appropriate currently established therapy (Ethical Review Procedures) ▪ If a procedure being studied is demonstrably superior, the control group should be offered the treatment promptly (Ethical Review Procedures) ▪ Randomization should be used only where there is 	<ul style="list-style-type: none"> ▪ Study findings should be communicated to the community and, where feasible, to individual subjects (Maximizing Benefit) ▪ During research in developing countries, health care or referrals to care should be provided and local health workers should be trained (Maximizing Benefit) ▪ Special care should be taken to avoid harm such

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<p><i>CIOMS Epidemiological Studies (cont.)</i></p>	<p>representatives from the community being studied (Ethical Review Procedures)</p> <ul style="list-style-type: none"> ▪ Individual and social perspectives should be considered in reviewing studies (Ethical Review Procedures) ▪ Both ethical and scientific aspects of a study should be considered (Ethical Review Procedures) ▪ Should be particularly vigilant of studies involving vulnerable populations (Ethical Review Procedures) ▪ Routine program evaluations need not be reviewed by an ethics review committee (Ethical Review Procedures) ▪ Investigators must submit detailed protocols (Ethical Review Procedures) ▪ Investigators should disclose any potential conflicts of interest to the ethics review committee (Conflict of Interest) 	<p>the well-being of the research subjects (General Ethical Principles)</p>	<p>customarily used in epidemiological studies (Informed Consent)</p> <ul style="list-style-type: none"> ▪ If informed consent is waived, investigator must safeguard confidentiality (Informed Consent) ▪ Individuals or their representatives should be informed that their data might be used in epidemiological studies and how confidentiality will be protected (Informed Consent) ▪ Consent is not required for use of publicly available information, but investigators must minimize disclosure of personal information (Informed Consent) ▪ Organizations and government agencies that have access by legislation or contract to data without consent must consider the ethics of using such data; access may be ethical where there is a minimal risk of harm to individuals, public benefit, and data confidentiality is protected (Informed Consent) ▪ Under certain circumstances, consent may be obtained from a community representative 	<p>(General Ethical Principles)</p> <ul style="list-style-type: none"> ▪ Class of persons that primarily will benefit from research should bear a fair proportion of research risks and burden (General Ethical Principles) ▪ Neither weaker members of communities nor dependent communities should bear disproportionate burdens of research (General Ethical Principles) ▪ Investigators must respect the culture and social mores of the community (Minimizing Harm) 	<p>should be stopped</p>	<p>genuine uncertainty regarding probable outcomes between/among regimens or procedures being studied, and subjects should be informed of the random allocation and uncertainty (Ethical Review Procedures)</p>	<p>as economic loss, stigmatization, or blame (Minimizing Harm)</p> <ul style="list-style-type: none"> ▪ Researchers should protect the confidentiality of personally identifiable information (Confidentiality) ▪ Compensation should be provided promptly for subjects inadvertently harmed by a study (Ethical Review Procedures) ▪ In externally funded studies, investigators must comply with the ethical rules of both the funding and the host countries, and should train health personnel in the host country (Ethical Review Procedures)

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<i>CIOMS Epidemiological Studies (cont.)</i>			(Informed Consent) <ul style="list-style-type: none"> ▪ An ethics review committee may approve selective disclosure of information when justified (Informed Consent) ▪ Undue influence should be neutralized (Informed Consent) ▪ Inappropriate inducements should not be used to obtain participation (Informed Consent) 				
Common Rule (45 C.F.R. § 46)	<ul style="list-style-type: none"> ▪ An IRB reviews and then approves, modifies, or disapproves research involving human subjects (§ 46.109) ▪ Institution may further review research approved by IRB, but may not approve research disapproved by the IRB (§ 46.112) ▪ IRB may terminate or suspend research if not conducted according to IRB requirements or if unexpected serious harm occurs to subjects or others. (§ 46.113) ▪ Cooperative research, may undergo joint review or rely on review by one or another IRB. Institution may further review 	<ul style="list-style-type: none"> ▪ Must minimize risk to subjects (§ 46.111(a)(1)) ▪ Risks must be reasonable in relation to anticipated benefits and importance of knowledge to be gained (§ 46.111) ▪ IRB should not consider effects of applying knowledge gained from the research. (§ 46.111) 	<ul style="list-style-type: none"> ▪ Generally required (§46.111), although IRB may alter or waive the requirement if necessary or if subject to approval by government officials for evaluation of public benefit program (§46.116) ▪ if minimal risk, no adverse effect on rights or welfare, not practicable to carry out research otherwise, additional information after participation (§46.116) ▪ Must be documented (§§46.111, -117) ▪ To be in form required by the IRB—written, summary, or oral (§46.117) ▪ IRB may waive the documentation 	<ul style="list-style-type: none"> ▪ Selection must be equitable, considering purpose and setting of research ▪ Must take into account special issues for vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically disadvantaged persons and include additional safeguards for these groups (§ 46.111) 	<ul style="list-style-type: none"> ▪ Required when appropriate (§ 46.111) ▪ IRB can terminate or suspend research if not conducted according to IRB requirements or is unexpected serious harm occurs to subjects (§ 46.113) ▪ IRB can terminate or suspend research if not conducted according to IRB requirements or is unexpected serious harm occurs to subjects (§ 46.113) 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ When appropriate, there should be provisions to protect personal privacy and confidentiality of data (§ 46.111)

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<i>Common Rule (cont.)</i>	research approved by IRB (§ 46.114)		requirement (§46.117) <ul style="list-style-type: none"> ▪ Must minimize coercion or undue influence (§46.116) ▪ Must be linguistically and culturally appropriate (§46.116) ▪ Must include research purpose, duration, description of procedures, identification of experimental procedures, description of risks, description of benefits, disclosure of alternative treatment, description of confidentiality of records, if any, explanation of compensation and available treatment of study-related injuries, contact information, statement of voluntariness ▪ Optional elements, to be included when appropriate: consequences of withdrawal, additional costs, circumstances under which participation will be terminated, approximate number of subjects (§46.116) 				
Belmont Report (1979)	<ul style="list-style-type: none"> ▪ Research activities should undergo review for the protection of human subjects (part A) 	<ul style="list-style-type: none"> ▪ Must present an assessment of risks and benefits laying out all relevant data, including probabilities and 	<ul style="list-style-type: none"> ▪ Should provide complete information about all risks, a reasonable volunteer would want to know about (part C) 	<ul style="list-style-type: none"> ▪ Cannot favor particular groups (part C) ▪ Burden placed on already burdened group must be appropriate (part C) 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ N/A

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<i>Belmont Report (cont.)</i>		<ul style="list-style-type: none"> ▪ magnitudes of possible risks and anticipated benefits (part C) ▪ Must consider possible psychological, physical, legal, social and economic harms and benefits (part C) ▪ Must reduce risks to those necessary to achieve research objective (part C) 	<ul style="list-style-type: none"> ▪ Consent must be voluntary—without undue influence or coercion (part C) ▪ Must ensure potential subjects understand the information (part C) ▪ Each population with limited capacity to consent (e.g. infants and young children, mentally disabled, terminally ill or comatose) should be addressed individually, allowing them choices and using third parties to act in the person's best interest, including withdrawing them from the study if necessary (part C) 	<ul style="list-style-type: none"> ▪ Need order of preference for subject selection (part C) ▪ Must have conditions for participation of certain subjects (e.g. institutionalized mentally infirm or prisoners) (part C) ▪ IRBs should consider distributive justice (part C) ▪ Must avoid using minorities, economically disadvantaged, seriously ill, or institutionalized individuals as subjects simply for administrative convenience (part C) ▪ Must acknowledge and respect autonomy and protect persons with diminished autonomy (part B) 			
Declaration of Helsinki (adopted 1964, last amended October 2000, clarified 2004) (#s refer to Basic Principles)	<ul style="list-style-type: none"> ▪ Research design and performance should undergo review (#13) 	<ul style="list-style-type: none"> ▪ Research must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature and other relevant sources of information, as well as adequate laboratory and, where appropriate, animal experimentation (#11) ▪ Must do risk benefit analysis prior to commencing research 	<ul style="list-style-type: none"> ▪ Participation should be limited to informed volunteers (#20) ▪ Preferably consent should be in writing (#9) ▪ Must ensure subject is informed of aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, anticipated benefits and potential risks and 	<ul style="list-style-type: none"> ▪ It must be reasonably likely that the study population will benefit from the research (#19) 	<ul style="list-style-type: none"> ▪ N/A 	<ul style="list-style-type: none"> ▪ Should test new methods against best current methods, but may use placebo or no treatment if there is no proven method (#29) ▪ Placebo may be used if there is a compelling, scientifically sound methodological reason why it is necessary, or if study is for a minor condition and use of a placebo poses no 	<ul style="list-style-type: none"> ▪ Must take steps to protect privacy and confidentiality (#21)

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<i>Declaration of Helsinki (cont.)</i>		project (#16 & 18) <ul style="list-style-type: none"> ▪ Must stop research if risks found to outweigh benefits (#17) 	potential discomfort (#22) <ul style="list-style-type: none"> ▪ Subject has the right to withdraw at any time (#22) ▪ Beware of duress or dependent relationship with physician (#23) ▪ If potential subject is incompetent, need informed consent from legal guardian; if a minor, need consent from both guardian and minor (#24) ▪ Incompetent persons and minors should be included only if research is for their benefit and cannot be done on competent adults (#24) ▪ If it is essential not to seek informed consent, must explain in protocol for approval by review committee (#26) 			additional risk of serious or irreversible harm (note of clarification on paragraph 29) <ul style="list-style-type: none"> ▪ All patients in study should be assured of access to best methods identified by study (#30) ▪ The access to best methods or other appropriate care must be described in the protocol (note of clarification on paragraph 30) 	