Comparison of Common Rule with the Declaration of Helsinki and Good Clinical Practice

The following chart was compiled by Toxicology Excellence for Risk Assessment (*TERA*) to provide a comparison of several sets of guidance regarding for the ethical treatment of human subjects. Key elements of the United States (US) government's "Federal Policy for the Protection of Human Subjects," generally referred to as the "Common Rule," are compared to the Declaration of Helsinki and Good Clinical Practice Guidelines.

The "Federal Policy for the Protection of Human Subjects," generally referred to as the "Common Rule," is specific to the US and was adopted by more than a dozen US agencies and departments in 1991, based on regulations first issued by the Department of Health and Human Services (45 CFR 46) and the Food and Drug Administration (21 CFR 50 and 56) in 1981 to protect human subjects. EPA has codified the Common Rule at 40 CFR 26.

The "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects" was drafted and adopted by the World Medical Association in 1964 and has been amended several times, most recently in October 2000 (World Medical Association 2000). The Declaration of Helsinki is "a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects" (World Medical Association, 2000; paragraph 1).

Good Clinical Practice (GCP) was prepared by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1997) and published by the US Food and Drug Administration (FDA) on May 9, 1997 (see 62 FR 25691). GCP was published with the objective of providing a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

REFERENCES

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1997. Good Clinical Practice: Consolidated Guideline. CPMP/ICH/153/95. Available at http://www.emea.eu.int/index/indexh1.htm (Select Topic E6, Step 5). Also published by the Food and Drug Administration (FDA) in the *Federal Register* at 62 FR 25691.

World Medical Association (WMA). 2000. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. First adopted in 1964; most recent revision in 2000. Available at http://www.wma.net/e/policy/17-c_e.html

Common Rule (CR) Elements (40 CFR 26)	Declaration of Helsinki (Adopted June 1964, amendments through October 2000)	Good Clinical Practice (GCP) Elements FR 62(90), May 9, 1997) and CPMP/ICH/153/95	Comments
Purpose The "Common Rule" is a **policy** that applies to all research involving human subjects that are conducted, supported, or otherwise "subject to regulation" by any federal department or agency. EPA limits the application of the Common Rule to studies conducted or funded by EPA.	***Purpose*** The World Medical Association has developed the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, as a statement of **ethical principles** to provide guidance to physicians and other participants in medical research on identifiable human material or identifiable data**.**	***Purpose*** Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. The GCP **guidelines** were published with the objective of providing a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.	This table compares elements of the Declaration of Helsinki and Good Clinical Practice (GCP) to provisions of the Common Rule (CR). Because of the diverse nature of the three documents, direct comparisons are not always possible. The Declaration of Helsinki is a statement of ethical principles, the Common Rule is a U.S. federal policy, and the GCP is explicit guidelines. The provisions set forth in the GCP guidelines were constructed consistent with the elements of the Declaration of Helsinki, therefore GCP should be consistent with the principles of Helsinki. GCP and Helsinki include provisions hat go beyond the Common Rule.
Applicability of the Common Rule **§26.101(a)** – This policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. **§26.101(b) --** provides exemptions to policy. **§26.101(h)** – When research covered by this policy takes place in foreign countries, procedures normally followed in foreign countries to protect human subjects may differ from those set forth in this policy (e.g., guidelines consistent with the Declaration of Helsinki amended 1989). In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the provisions set forth in the CR.	***Applicability of the Declaration of Helsinki*** **Prin. 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. **Prin. 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.	***Applicability of GCP*** **FR 62(90) Introduction –** Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. The GCP guidelines were published with the objective of providing a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. As such, the guidance states that this guideline should be followed by investigators generating clinical trial data that are intended for submission to regulatory authorities. The principles established in the guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects. **§1.24 -** GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.	The Common Rule (CR) applies to all research involving human subjects that are conducted, supported, or otherwise "subject to regulation" by any federal department or agency. EPA does not consider data developed by private parties in support of pesticide registrations under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and that are not conducted or supported by federal agencies, to constitute "research subject to regulation"; rather, EPA limits application of the Common Rule to studies conducted or funded by EPA. Accordingly, the Common Rule does not apply to such research at this time. Such research, however, is subject to certain informed consent requirements and requirements for voluntary participation prescribed by FIFRA. While CR is set forth as an express requirement for federal research involving human subjects, the published GCP is a guideline providing recommended protocols for acceptable clinical trials involving human subjects. The provisions set forth in the GCP guidelines were constructed consistent with the elements of the Declaration of Helsinki. The CR (**§26.101(h)** indicates the possibility of accepting alternative study guidelines (for studies performed in other countries), such as those consistent with the Declaration of Helsinki.
Requirements of the CR **§26.111(a)(4) –** Investigators must receive informed consent from human subjects participating in the proposed study. **§26.107 –** An IRB must be established. The term IRB is defined in **§26.102(g)** as an institutional review board that must be established for review of human research subject to the CR. **§26.103 –** CR requires that institutions engaged in research	***Requirements of Declaration of Helsinki*** Only the Helsinki principles directly related are listed here. Helsinki contains numerous principles not covered by the CR. **Prin. 20**. The subjects must be volunteers and informed participants in the research project. **Prin. 13**. Provides for review and approval of protocol,	***Requirements of GCP*** Only the GCP requirements equivalent to those of the CR have been summarized here, as the GCP has more breadth of coverage than the CR provisions. **FR 62(90), §4.8 –** Investigators must obtain informed consent from prospective trial subjects. **§3 –** An Institutional Review Board/Independent Ethics	The basic requirements of the CR for informed consent and ethical review are present in the GCP guidelines and Declaration of Helsinki.

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involving human subjects and conducted or supported by a Federal department or agency provide written assurance deemed acceptable by the department or agency that the institution will comply with the requirements set forth in the CR (including designation of an IRB and the establishment of written procedures for the IRB) and provide certification of compliance.	where appropriate, by a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence.	Committee (IRB/IEC) should be formed to review and approve proposed research. The term IEC is defined in **§1.27** and IRB in **§1.31**. **§5.1.1 –** The sponsor of the proposed research is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures (SOPs) to ensure that trials are conducted, documented, and reported in compliance with protocol, GCP, and applicable regulations.	
IRB Functions and Operations - **§26.108(b) –** to review proposed research at convened meetings at which a majority of members are present, with at least one member whose primary concerns are in nonscientific areas. Approval of proposed research requires a majority of the members present at the meeting.	***Helsinki Functions and Operations*** Declaration of Helsinki is a statement of principles and as such does not provide explicit details of ethical committee operations. **Prin. 13**. Provides for review and approval of protocol by specially appointed ethical review committee, where appropriate, and for the committee's right to monitor ongoing trials. This ethical committee should be in conformity with the laws and regulations of the country in which the research experiment is performed.	***IRB/IEC Functions and Operations*** **FR 62(90), §3.1.1 –** An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects. **§3.2.2 –** The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its regular meetings, and should comply with GCP and applicable regulatory requirements. **§3.2.3 –** The IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.	IRB functions and operations are similar in both the CR and GCP.
IRB Membership – **§26.107(a) –** required minimum of five members of varying backgrounds. **§26.107(b) –** no IRB can be entirely made up of members of one gender or one profession. **§26.107(c) –** IRB must have at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are nonscientific areas. **§26.107(d) –** IRB must have at least one member not otherwise affiliated with the institution performing, supporting, or regulating the proposed research. **§26.107(e) –** no IRB may have a member participating in initial or continuing review of any project in which the member has a conflicting interest. **§26.107(f) –** IRB may invite individuals with competency in specialized areas in the review of projects involving expertise beyond that of the IRB members. These individuals may not vote with the IRB.	***Specially Appointed Ethical Review Committee*** **Prin. 13**. Specially appointed ethical review committee must be independent of the investigator, the sponsor or any other kind of undue influence.	***IRB/IEC Membership*** **FR 62(90), §3.2.1 –** The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include: (a) At least 5 members. (b) At least one member whose primary area of interest is in a nonscientific area. (c) At least one member who is independent of the institution/trial site. Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter. A list of IRB/IEC members and their qualifications should be maintained. **§3.2.6 –** The IRB/IEC may invite nonmembers with expertise in special areas for assistance. But according to **§3.2.4**, only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.	The provisions for IRB membership are generally equivalent between the CR and GCP. However, no restriction is made in the GCP guidelines regarding the prohibition of an IRB totally composed of members of one gender, as is addressed by the CR. Helsinki does not provide details of membership of the ethical committee.
IRB Review and Approval of Research, and Ongoing Review **§26.109(a) –** An IRB is required to review and has the authority to approve, require modifications in, or disapprove all research activities covered by the CR.	***Ethical Committee Review*** **Prin. 13**. A specially appointed ethical review committee should approve the protocol, where appropriate. The committee has the right to monitor	***IRB/IEC Review and Approval of Research, and Ongoing Review*** **FR 62(90), §3.1.2 –** The IRB/IEC should obtain the relevant documents (e.g., trial protocol(s)/amendment(s),	The review and approval provisions for the IRB are essentially equivalent between the CR and GCP. Helsinki principles do not go into detail on this subject.

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§26.109(d) – An IRB must provide written notification to the investigator(s) and institution regarding its decision to approve or disapprove the proposed research or of any modifications required for approval. **§26.109(e) –** An IRB must also conduct continuing review of research covered by the CR at intervals appropriate to the degree of risk associated with the study, but not less than once per year. **§26.110(b) –** An IRB may use expedited review procedures to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk; (2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.	ongoing trials. The researcher has the obligation to provide monitoring information to the ethical committee, especially for any serious adverse events.	written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures, written information to be provided to subjects, etc.). The IRB/IEC should review a proposed clinical trial within a reasonable time and document its view in writing, clearly identifying the trial, the documents reviewed, and the dates for the following: favorable opinion; modifications required prior to its approval/favorable opinion; disapproval/negative opinion; and termination/suspension of any prior approval/favorable opinion. **§3.1.3 –** The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented in the investigator's current curriculum vitae or other documentation. The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.	The CR gives express attention to the conditions for expedited review of research by an IRB, whereas the GCP guidelines only provide a general reference to expedited review as a procedural issue needing to be accounted for in the IRB/IEC's establishment and documentation of procedures. The GCP reference to expedited review is as follows: **FR 62(90), §3.3.5 –** Providing, according to the applicable regulatory requirements, **expedited review** and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.
Criteria for IRB Approval of Research **§26.111(a)(1) through (a)(7) –** An IRB may not approve research subject the CR unless it determines that all of the proposed research satisfies the following requirements: • **Risks to subjects are minimized** by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. • **Risks to subjects are reasonable** in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. • **Selection of subjects is equitable**, taking into account the purposes of the research and the setting in which the research will be conducted, and the special problems of research involving vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or otherwise economically or educationally disadvantaged persons. • **Informed consent** has been sought, obtained from subjects and documented in accordance with the CR. • When appropriate, the research plan makes adequate provision for monitoring the data collected to **ensure the safety of subjects**. • When appropriate, there are adequate provisions in the research plan to **protect the privacy of subjects** and maintain confidentiality of data. **§26.111(b) –** When some or all of the subjects are likely to be vulnerable to coercion or undue influence, the IRB must ensure that additional safeguards have been included in the study to protect those individuals.	***Principles of Declaration of Helsinki*** **Prin. 13**. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol, which should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee. **Prin. 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. **Prin. 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. **Prin. 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. **Prin. 16.** Every medical research project involving	***Principles of GCP*** **FR 62(90), §2** **§2.1 –** Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirements. **§2.2 –** Before trial initiation, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks. **§2.3 –** The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. **§2.4 –** The available nonclinical and clinical information on an investigation product should be adequate to support the proposed clinical trial. **§2.5 –** Clinical trials should be scientifically sound, and described in a clear, detailed protocol. **§2.6 –** A trial should be conducted in compliance with the protocol that has received prior IRB/IEC approval. **§2.7 –** The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist. **§2.8 –** Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s). **§2.9 –** Freely given informed consent should be obtained from every subject prior to clinical trial participation.	There is consistency in the stated principles of Helsinki, GCP and the established criteria for IRB approval of proposed research. The GCP guidelines delineate the responsibilities and basic procedural guidelines for IRB/IECs but do not provide explicit approval criteria as set forth in the CR.

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	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. **Prin 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. **Prin 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. **Prin 20**. The subjects must be volunteers and informed participants in the research project. **Prin 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.	**§2.10 –** All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. **§2.11 –** The confidentiality of records that could identify subjects should be protected in accordance with applicable regulatory requirements.	
IRB Procedural Requirements **§26.103(b)(4) –** Written procedures that the IRB will follow must be documented as part of the assurance of compliance with the CR. These procedures relate to the following: (i) conduct of initial and continuing review of research and reporting its findings and actions to the investigator and the institution; (ii) determination of which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) ensuring prompt reporting to the IRB of proposed changes in a research activity, and ensuring that such changes in approved research may not be initiated without IRB approval except when necessary to eliminate apparent immediate hazards to the subject. **§26.103(b)(5) –** Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and	***Ethical Committee Procedural Requirements*** Declaration of Helsinki is a statement of principles, and as such does not detail procedural requirements for the ethical committee beyond those items noted above.	***IRB/IEC Procedural Requirements*** **FR 62(90), §3.3 –** The IRB/IEC should establish, document in writing, and follow its procedures, which should include: **§3.3.1 –** Determining its composition (names and qualification of members) and the authority under which it is established. **§3.3.2 –** Scheduling, notifying its members of, and conducting its meetings. **§3.3.3 –** Conducting initial and continuing review of trials. **§3.3.4 –** Determining the frequency of continuing review. **§3.3.5 –** Providing expedited review and approval of minor changes in ongoing research already approved by the IRB/IEC. **§3.3.6 –** Specifying that no subject should be admitted to a trial before the IRB/IEC issues approval of the trial. **§3.3.7 –** Specifying that no deviations from or changes of protocol should be initiated without prior written IRB/IEC approval.	The basic IRB procedural requirements of the CR appear to be present in the more detailed guidelines of GCP. GCP addresses items such as documentation of IRB/IEC membership and scheduling of meetings that the CR does not address specifically. In addition, greater detail is given in the GCP as to specific requirements of investigator notification of the IRB/IEC of unexpected circumstances or emergencies as well as to the reporting requirements of the IRB/IEC.

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(ii) any suspension or termination of IRB approval.		**§3.3.8 –** Specifying that the investigator should promptly report to the IRB/IEC: (a) Deviations from or changes of protocol to eliminate immediate hazards to trial subjects. (b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial. (c) All adverse drug reactions that are both serious and unexpected. (d) New information that may affect adversely the safety of the subjects or the conduct of the trial. **§3.3.9 –** Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning: (a) Its trial-related decisions/opinions. (b) The reasons for its decisions/opinions. (c) Procedures for appeal of its decisions/opinions.	
Review by Institution **§26.112 –** Research subject to the CR that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. Such officials, however, may not approve research not approved by an IRB.	***Obligations of Authors and Publishers*** **Prin. 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.	***Sponsor Confirmation of Review by IRB/IEC and Monitoring*** **FR 62(90), §5.11.1 –** The sponsor of the proposed research should obtain from the investigator/institution elements such as the name and address of the investigator's/institution's IRB/IEC, a statement that the IRB/IEC is organized and operational, documentation of review protocol, etc., and the statement of the IRB/IEC's approval of the proposed research. **§5.11.2 –** If the IRB/IEC conditions its approval upon changes in any aspect of the trial, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date that approval was given by the IRB/IEC. **§5.11.3 –** The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/reevaluations with favorable opinion, and of any withdrawals or suspensions of favorable opinion. **§5.18 –** The sponsor has the responsibility of appointing qualified monitors and to ensure that trials are adequately monitored to verify that the rights and well being of subjects are protected, the reported trial data are accurate, complete and verifiable, and that the conduct of the trial is in compliance with protocol, GCP, and applicable laws and regulations. **§5.19 –** The sponsor may perform periodic auditing of the trial in addition to routine monitoring for quality assurance purposes, to evaluate trial conduct and compliance with protocol, SOPs, GCP, and applicable laws and regulations. **§5.20 –** If either the monitoring or auditing efforts indicate serious and/or persistent noncompliance on the	The CR provides for further review by the institution of the decision for approval of research by the IRB, with the institution having authority to reverse IRB approvals if deemed appropriate, but without the ability to reverse IRB disapprovals. The GCP guideline places the burden on the "sponsor" for review of the IRB/IEC decision as well as QA/QC monitoring/auditing of trial conduct by the "investigator/institution". Helsinki does not address review by the institution, but does contain a principle regarding publication of studies. There is some difficulty in comparing the CR and GCP provisions due to the semantics regarding the terms "sponsor," "institution," and "investigator/institution." The CR generically defines an "institution" as any public or private entity or agency (including Federal, State, and other agencies) (**40 CFR §26.102(b)**). The GCP guidelines define an "investigator as the person responsible for the conduct of the clinical trial at the trial site (**FR 62(90) §1.34.** The GCP guidelines define an "investigator/institution" as meaning "the investigator and/or institution, where required by the applicable regulatory requirements" (**FR 62(90), §1.35**). The GCP definition of "sponsor" is "an individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial" (**§1.53**).

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		part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial.	
Documentation of IRB Activities **§26.115(a) and (b) –** An institution, or when appropriate and IRB, shall prepare and maintain adequate documentation of IRB activities including: (1) copies of research proposals reviewed, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects; (2) minutes of IRB meetings with the detail specified in **§26.115(a)(2)** of the CR; (3) records of continuing review activities; (4) copies of all correspondence between the IRB and the investigator(s); (5) list of IRB members; (6) the written procedures for the IRB; and (7) statements of significant new findings provided to subjects. Records required by the CR must be retained for at least 3 years, and records relating to the research being conducted must be retained at least three years after completion of the research.	***Documentation of Ethical Committee*** Declaration of Helsinki is a statement of principles, and as such does not detail procedural requirements for the documentation of ethical committee activities.	***IRB/IEC Record-keeping*** **FR 62(90), §3.4 –** The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least three years after completion of the trial and make them available upon request from the regulatory authority(ies). The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.	Record-keeping for the IRB/IEC under the CR and GCP are nearly equivalent. Helsinki principles do not address record-keeping.
General Requirements for Informed Consent **§26.116 –** For research projects subject to the CR, investigator(s): • Must obtain legally effective informed consent from any human subject or the subject's legally authorized representative. • Must seek consent only under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. • Must provide information to the prospective subject that is expressed in understandable language. • Must not include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or language that releases or appears to release the investigator, the study sponsor, the institution, or its agents from liability for negligence. The same section sets forth statements that must be provided to subjects regarding informed consent: • A statement that the study involves research, an explanation of the purposes of the research, and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental. • A description of any reasonably foreseeable risks or discomforts to the subject. • A description of any benefits to the subject or to others that may reasonably be expected from the research. • A disclosure of appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the subject. • A statement describing the extent, if any, to which	***Principles Regarding Informed Consent*** **Prin 20**. The subjects must be volunteers and informed participants in the research project. **Prin 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. **Prin. 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. **Prin. 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	***Informed Consent of Trial Subjects*** **FR 62(90), §4.8** **§4.8.1 –** In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects. **§4.8.2 –** The written informed consent form and any other written information to be provided to subjects should be revised, subject to IRB/IEC approval, whenever important information becomes available that may be relevant to the subject's consent. The subject or legally authorized representative should be informed of new information in a timely manner to ensure informed consent. **§4.8.3 –** Neither the investigator nor the trial staff should coerce or unduly influence a subject to participate or to continue to participate in a trial. **§4.8.4 –** None of the oral and written information concerning the trial including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence. **§4.8.5 –** The investigator or designated representative	Elements of informed consent are relatively equivalent between the CR and GCP, with the GCP guidelines providing a more detail. Details such as payment issues are dealt with in the GCP guidelines but scarcely mentioned in the CR. The Helsinki principles cover most of these elements, but do not explicitly address disclosure of alternative procedures, compensation, and some of the additional enumerated elements (e.g., number of participants).

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confidentiality of records identifying the subject will be maintained. • For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where to obtain additional information. • An explanation of whom to contact for answers to questions about the research and the subjects' rights and whom to contact in the event of a research-related injury to the subject. • A statement that participation is voluntary, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. • When appropriate, one or more additional enumerated elements of informed consent shall be provided to each subject as specified in **§26.116(b)**, including: (1) a statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable; (2) anticipated circumstances under which the subject's participation may be terminated with subject's consent; (3) any additional costs to the subject resulting from participation; (4) the consequences of a subject's decision to withdraw and procedures for orderly termination of participation by the subject; (5) a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue in the research will be provided to the subject; and (6) the approximate number of subjects in the study. **§26.116(c) and (d)** outline circumstances when informed consent may be waived or which may be altered.	relationship. **Prin 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.	should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval by the IRB/IEC. **§4.8.6 –** The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or subjects legally acceptable representative and the impartial witness, where applicable. **§4.8.7 –** The subject or legally acceptable representative should be given ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions of the subject or legally acceptable representative regarding the study should be answered satisfactorily. **§4.8.10 –** Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: (a) That the trial involves research. (b) The purpose of the trial. (c) The trial treatment(s) and the probability for random assignment to each treatment. (d) The trial procedures to be followed, including all invasive procedures. (e) The subject's responsibilities. (f) Those aspects of the trial that are experimental. (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant. (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this. (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks. (j) The compensation and/or treatment available to the subject in the event of trial-related injury. (k) The anticipated pro-rated payment, if any, to the subject for participating in the trial. (l) The anticipated expenses, if any, to the subject for participating in the trial. (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw at any time without penalty or loss of benefits to which the subject is otherwise	

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		entitled. (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records without violating the confidentiality of the subject, and that by signing the informed consent form, the subject is authorizing such access. (o) That records identifying the subject will be kept confidential. (p) That the subject or legal representative will be informed in the event of new information that may be relevant to the subject's willingness to continue participation. (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of a trial-related injury. (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. (s) The expected duration of the subject's participation in the trial. (t) The approximate number of subjects involved in the trial. **§4.8.13 –** A nontherapeutic trial, with no anticipated direct clinical benefit to the subject, should be conducted in subjects who personally give consent and who sign and date the written informed consent form – unless conditions set forth in **§4.8.14** are fulfilled. **§4.8.15 –** In emergency situations, when prior consent of the subject is not possible, the legal representative should provide consent. If the representative is not available, then enrollment of the subject should require measures described in the protocol and approved by the IRB/IEC, with prompt notification of the subject's legal representative.	
Documentation of Informed Consent **§26.117(a) through (c) –** The investigator(s) must document informed consent as follows: • Informed consent must be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's authorized representative, and a copy must be provided to the person signing the form. • Either a long or a short form written consent document may be used, under the specified conditions, as described below. • The long form must include the elements of informed consent required by the CR. While this form may be read to the subject or representative, the investigator must give either the	***Principles Related to Documentation of Informed Consent*** **Prin 22.** 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. **Prin 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	***GCP Documentation of Informed Consent*** **§4.8.8 –** Prior to the subject's participation, the written informed consent form should be signed and personally dated by the subject or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. **§4.8.9 –** If a subject or legal representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the consent form has been signed, if possible, by the subject or legal representative, the form should be signed by the witness to ensure that the information in the consent form and	Documentation of informed consent is very similar between the CR, Helsinki, and the GCP guidelines, but the GCP does not discuss provisions for variations of consent forms such as long forms and short forms. Helsinki does not address providing subjects with a copy of the consent form.

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subject or the representative adequate opportunity to read the form before it is signed. • If the short form is used, it must state that the elements of informed consent required by the CR have been presented orally to the subject or the subject's legally authorized representative. When the short form is used, there must be a witness to the oral presentation and the IRB must approve a written summary of what is to be orally stated to the subject or the representative. While only the short form itself is to be signed by the subject or representative, the witness must sign both the short form and a copy of the summary, and the person actually obtaining consent must sign a copy of the summary. A copy of both the short form and the summary must be given to the subject or representative. • An IRB may waive the requirement for signed consent form under certain conditions outlined in **§26.117 (c).**	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. **Prin. 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.	any other written information was accurately explained to and apparently understood by the subject or legal representative. **§4.8.11 –** Prior to participation, the subject or legal representative, should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects, including any amendments to the written information. **§4.8.12 –** When a clinical trial includes subjects who can only be enrolled in the trial with the consent of the subject's legal representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.	
Written Assurance **§26.103(a) through (f) –** Each institution engaged in research that is covered by the CR and is conducted or supported by a Federal department or agency must provide written assurance satisfactory to the department or agency head that the institution will comply with the requirements set forth in the CR. Among other things, the assurance must include: • A statement of principles governing the institution with regard to protecting the rights and welfare of human subjects of research. • Designation of one or more IRBs established in accordance with the CR, with an identification of IRB members and a description of relevant backgrounds. • The written procedures which the IRB must follow. The regulations specify in detail the required contents of these procedures, including those that ensure prompt reporting of any unanticipated problems with the research involving risks to human subjects. • The department or agency head will take into consideration a number of factors, including the adequacy of the proposed IRB in light of the anticipated scope of research activities, in determining whether to approve or disapprove the assurance or enter into negotiations for an approvable assurance. An institution with an approved assurance must certify that each application or proposal for research covered by the assurance and not exempted or waived has been reviewed and approved by the IRB.	No similar concepts are included in the Declaration of Helsinki. Its focus is on the responsibilities of the physician. See below for principles regarding medical research combined with medical care.	***Quality Assurance*** **FR 62(90), §5.1.1** indicates that the sponsor is responsible for maintaining quality assurance with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with protocol, GCP, and applicable regulations.	Equivalent language as set forth in the CR requiring an institution to submit written assurance of compliance with the policy in question to a regulatory department or agency is not present in the GCP guidance. The GCP does not have a directly comparable requirement, but does address general quality assurance/quality control (QA/QC) concerns and places the burden of responsibility for assurance of QA/QC and compliance with GCP on the sponsor.