

Public Policy Statement: Clinical Trial Ethics

Purpose

As a global healthcare company, Merck's role is first and foremost to discover, develop and provide innovative products and services that save and improve lives around the world. Merck, known as MSD outside of the United States and Canada, conducts and supports clinical trials worldwide to evaluate the safety and efficacy of our products. These trials are fundamental to the development of innovative medicines and vaccines that treat and prevent illness.

Merck is committed to developing novel medicines and vaccines that are relevant for global human health. Achieving this requires Merck to expand its focus beyond the geographic regions that have historically served as the primary focus of our research and development activities. Merck also recognizes that the successful development and introduction of important new therapeutic and preventive products requires us to adapt to variability in national regulatory requirements, as well as to socioeconomic and cultural differences among countries. This effort embraces collaboration with diverse partners to assure that clinical research is properly structured.

Conducting clinical trials globally may also enable Merck to bring innovative medicines and vaccines to market more rapidly in countries with disproportionate disease burden, assess product efficacy in diverse populations, and contribute to the development of research and clinical capabilities in emerging and developing countries.

Merck is committed to conducting clinical trials globally according to the same high ethical standards. We developed the position below to clarify and guide our approach to clinical trial ethics, which we will incorporate into our operational policies and research and development plans.

Scope

- This statement applies globally to Merck sponsored clinical trials, including clinical trials administered by contract research organizations (CROs) or academic research organizations on Merck's behalf, and clinical trials undertaken through joint ventures and other partnership arrangements.
- The statement also applies to assuring that proposals reviewed by the Merck Investigator Initiated Studies Program Review Committees meet an acceptable scientific and ethical standard (recognizing that the subsequent conduct of studies funded through this program is the fundamental responsibility of the external investigator).

Merck Position

- Merck applies the same ethical standards to clinical trials in all countries including the developing world, in accordance with the global standards of the International Conference on Harmonization - Good Clinical Practices (ICH-GCP), the Council for International Organizations of Medical

Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 2002), the Pharmaceutical Research and Manufacturers of America (PhRMA, 2009) Principles on Conduct of Clinical Trials, applicable local regulatory requirements and following the ethical principles that have their origin in the Declaration of Helsinki.

- Merck complies with all laws and regulations in countries where we conduct clinical trials and where we market our products, and works closely with national and local authorities to provide information to demonstrate this compliance.

Ethics Committee Review

- Merck carries out clinical trials only following approval by Ethics Review Committees with appropriate jurisdiction.

Protocol

- All clinical studies sponsored by Merck must have a written plan that describes the scientific, administrative, and regulatory aspects of the study in a manner that is consistent with currently accepted scientific methodology, Good Clinical Practices and appropriate regulatory requirements.
- Merck conducts clinical trials based on scientifically sound protocols that take into account the potential risks to the research participant along with the possible benefit to the participant and to society. Scientific, ethical and clinical judgments must guide and support the design of the clinical trial, particularly those aspects directly affecting the research participants.
- Merck is committed to studying our medicines and vaccines in diverse racial, gender and ethnic populations, and to achieving this in part through broadening the diversity of the clinical investigators that we engage in our studies.

Informed Consent

- Merck requires that all investigational studies in human subjects be carried out in a manner respectful of the local culture and consistent with legal statutes and regulations for the protection of human subjects. Merck requires assurances that subjects and/or their legal representatives understand the procedures, use and any potential disclosure of personal health information, any potential use of biological samples beyond routine testing, risks/benefits involved in a study, alternatives to trial participation, and that their participation is voluntary. The subjects will be informed of the provision of planned post study care and/or product supply, if any, during the informed consent process.
- Consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research. The informed consent procedures and consent form documents for any clinical study must conform to all relevant legal statutes and governmental regulations concerning research in human subjects and the privacy and security of medical information. Consent information should be communicated in a manner that ensures both compliance with local regulatory requirements and the research subject's understanding (e.g. local language).
- The consent information and its presentation must comply with all applicable regulations pertinent to where the data will be submitted and collected.

The elements of the consent form must be consistent with those of the International Conference on Harmonization Good Clinical Practices Document.

- During the course of the trial, the subject must be made aware of any significant new information that may affect the subject's willingness to continue participation in the trial.

Use of Placebo Controls

- Merck adheres to Council for International Organizations of Medical Sciences (CIOMS, 2002) Guideline 11, "Choice of control in clinical trials" when determining the intervention used with control group participants in a clinical trial. Guideline 11 is reproduced below:
- As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo.

Placebo may be used:

- when both patients receiving test vs. placebo also receive the full standard of care (that is, the test vs. placebo is in addition to standard therapy);
 - when there is no established effective intervention;
 - when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;
- or
- when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not invoke an important risk of serious or irreversible harm to the subjects.

Study Monitoring

- Merck conducts worldwide investigational study monitoring to ensure that all clinical studies sponsored by Merck are conducted and reported in compliance with the approved protocol/amendments(s), Merck policies, Good Clinical Practices (GCPs), and with applicable country and state specific regulatory requirements(s). While Contract Research Organizations (CROs) conducting Merck-sponsored trials may use their own procedures, these procedures are reviewed and approved by Merck to ensure they meet regulatory requirements and adhere to Merck's clinical trials ethical principles. Merck also maintains oversight of CRO activities. An inherent part of monitoring is to ensure that the rights and well being of human subjects are protected, and the trial data are reported in an accurate, complete, and verifiable fashion compared to source documents.

Standard of Care, Post Study Care and Availability of Medication

- Merck intends for its clinical trials to be responsive to the health needs and priorities of the populations and communities in which they are carried out. This includes consideration to making any intervention or product developed, or knowledge generated as a result of clinical trial research, reasonably available for the benefit of that population or community, consistent with CIOMS Guideline 10, "Research in Populations and Communities with Limited Resources".

- Merck recognizes that governments have responsibility for ensuring that their citizens have equitable access to high-quality health care services, including the provision of medicines and vaccines. In general, the provision of post trial care for clinical trial participants continues under the applicable health care system of the host country.
- When clinical trials are carried out in countries or communities with limited resources, the sponsor must determine the appropriate standard of care to be provided to clinical trial participants, including determining whether or not an investigational agent will be made available after the clinical trial to trial participants, and determining whether or not other services provided during a clinical trial will continue after the trial, and under what circumstances. This also applies to investigation of new indications for licensed medicines. At minimum, health care services will be provided to the local standard of care where the trial is conducted, and will be sufficient to ensure the clinical trial will be conducted safely.
- Merck will work to ensure the reasonable availability of investigational drugs, new indications for licensed medicines and any associated health care services following completion of a study, consistent with CIOMS guidelines. Given the complexity of factors that may determine the nature of "reasonable availability" of an investigational agent or a new indication for a licensed medicine, the measures taken following individual studies will need to be decided on a case by case basis and may at times include consideration of the provision of other therapeutics available in a country. Among the factors to be considered are the certainty of the benefit/risk of the investigational product given the state of the development program, the approval status of the product or indication in the countries where it is being studied, the length of time the investigational agent and/or services will be provided to clinical trial participants or to the community or population in question, the severity of a subject's medical condition, the effects, if any, of withdrawing the agent or service (including apparent prior individual therapeutic response), the cost to the participant or health system of continuing the agent or service, and the ability to monitor the patient following completion of the clinical trial.
- When an investigational product or new indication for a licensed product has significant potential to address a health care need in a host country, Merck will consult with appropriate stakeholder representatives in the country for input on considerations on the definition of reasonable availability for the particular clinical trial. The stakeholder representatives might include the national government, health ministry, local health authorities, investigators, scientific and ethics groups, and representatives of the community from which clinical trial participants are drawn.
- Merck will address the issue of ancillary care (medical issues arising in the course of a trial but which are unrelated to it) on a situational basis

Clinical Trial Registration and Results

- Merck complies with laws requiring registration of clinical trials and disclosure of clinical trial results, and is committed to the transparency of the clinical trials we sponsor.
- Since 2007, Merck has registered, at trial initiation, all clinical trials in patients (Phases I-V) that the company sponsors and conducts worldwide on www.ClinicalTrials.gov. We also disclose results from all registered clinical trials of marketed products – regardless of outcome – on www.ClinicalTrials.gov.

Registration of Product

- When addressing whether to conduct a clinical trial in a particular developing country, it is Merck's intent to pursue registration of the product in the countries where the trial is conducted. Where a product is studied in a developing country and registration is delayed or is not ultimately pursued, Merck will work to assure access to the product for participants who achieved meaningful benefit. This approach is specifically intended to assure that benefit is provided to trial participants in resource-limited settings.
- We will work to initiate registration of our products in all countries where there is a public health need in a timely manner in conjunction with local regulatory authorities.
- We will work with the World Health Organization to pre-qualify our products, where appropriate, to expedite access in low income countries.

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