IMPLEMENTING CLINICAL RESEARCH IN VIETNAM:

A DIALOGUE ON THE CURRENT REGULATIONS OF THE MINISTRY OF HEALTH

SYMPOSIUM PROCEEDINGS

A two-day workshop organized by Vietnam Ministry of Health

12-13 July 2007, Hanoi, Vietnam

fhi Family Health International

VIETNAM
MINISTRY OF HEALTH

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Abbreviations and Acronyms

ADR	Adverse Drug Reaction
CIOMS	Council for International Organization of Medical Sciences
CFR	Code of Federal Regulations
CPP	Certificate of Pharmaceutical Product
CRA	Clinical Research Associate
DAD	Drug Administration Department
DPF	Department of Planning and Finance
DST	Department of Science and Training
EC	Ethics Committee
FDA	U.S. Food and Drug Administration
FSC	Free Sales Certificate
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCMC	Ho Chi Minh City
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INGO	International Non-Governmental Organization
IRB	Institutional Review Board
M&E	Monitoring and Evaluation
MOH	Ministry of Health
MPI	Ministry of Planning and Investment
NGO	Non-Governmental Organization
PACCOM	People's Aid Coordinating Committee
PHS	Provincial Health Services
PI	Principal Investigator
PM	Prime Minister
SOP	Standard Operating Procedure
VUFO	Vietnam Union for Friendship Organizations
WHO	World Health Organization

Preface

Three departments within Vietnam's Ministry of Health—the Departments of Science and Training, Finance and Planning, and Drug Administration—joined together in July 2007 to present a two-day introductory workshop on Vietnam Government's Regulations on Clinical Research. Attending the workshop were approximately 60 doctors and other hospital staff from throughout the country, all of whom are working on international clinical trials at their hospital sites.

The workshop covered various aspects of clinical research, including the important role of ethics—an area that clinic site personnel, and physicians in particular, must understand when asking patients to participate in a new drug study. The workshop also covered guidance for hospitals regarding the process which must be followed to seek MOH approval for new study protocols; the process of importing drugs and supplies needed to conduct the study; and the close monitoring of patient safety which is required for all clinical studies in Vietnam.

As it has become evident that there is a need for improved clinical research study oversight in Vietnam as well as capacity building in research ethics and good clinical practices, the Ministry of Health will soon publish a document describing Guidelines for Clinical Research in Vietnam which provides a detailed endorsement of internationally accepted guidelines on clinical research and research ethics. The MOH is also in the process of developing inclusive operational guidance to meet the increasing demands in clinical research in Vietnam while ensuring adherence to strict technical and ethical requirements.

We thank Family Health International (FHI) for their guidance and support for the workshop and look forward to working with all local and international partners in improving the conduct of clinical research in Vietnam.

Prof. Dr. **Truong Viet Dung**

Director
Department of Science and Training- Vietnam Ministry of Health

In July 2007 a two-day workshop was held in Hanoi in which representatives from the Ministry of Health presented government regulations and procedures for conducting clinical research in Vietnam. Attending this workshop were approximately 60 medical professionals from institutions in Vietnam who participated as representatives from sites conducting international multi-center clinical research. Since internationally sponsored clinical trials are relatively new in Vietnam and the appropriate processes have not always been clear to investigators and medical centers, the purpose of the workshop was to clarify these procedures and open a dialogue between the Ministry of Health and clinical research sites.

Family Health International (FHI) has worked for over 10 years in Vietnam in the fields of reproductive health, HIV/AIDS, and clinical research in numerous infectious disease areas. FHI's clinical research team has expanded within the past two years and now includes capacity building to clinical site staff on research ethics and Good Clinical Practice (GCP). Other training has been provided, including protocol implementation, regulatory management and many other aspects of clinical trials operations.

We would like to acknowledge the Ministry of Health representatives who presented the material and were open to questions and comments from investigators from research sites throughout the country. We are also grateful to the clinical study site staff that have been present and shared their experience in conducting clinical research trials in Vietnam so far.

We see this meeting as an important step in the ongoing development of the practice of clinical research in Vietnam.

Stephen Mills, MPH., PhD

Country Director
Family Health International/Vietnam

Approval of protocol, monitoring and evaluation, final review, and dissemination of research

Nguyen Ngo Quang, MSc.
Department of Science and Training, Vietnam Ministry of Health

This presentation reviews important issues in

- the current approval process for clinical research protocols in Vietnam
- current regulations for conducting clinical trials in Vietnam

There are several legal and regulatory provisions in Vietnam describing different aspects of the process by which a clinical research protocol should be submitted for approval and implementation. These laws also address evaluation. They are, however, often fragmented and insufficient. Before January 11, 2007, there was no law regulating clinical trials. But the Vietnam Ministry of Health (MOH) is engaged in the process of developing inclusive operational guidance to meet increasing demands in clinical research in Vietnam while ensuring adherence to strict technical and ethical requirements.

Preambles to regulations for clinical research

- The Pharmaceutical Law, issued in June 2005
- Decision No. 186/BYT-QD, issued May1975 on Guidelines for clinical trials and treatment
- Decision No. 371/BYT-QD, March 1996 on Guidelines for Evaluation of Safety and Efficacy of Traditional Medicines
- Helsinki Declaration 1986
- WHO Guidelines for Good Clinical Practice (GCP) and ECB
- ICH Harmonized Tripartite Guidelines for Good Clinical Practice E6
- Protection of Human Subjects and Research efficacy
- Ensuring Good Clinical Practice standards in clinical trials in Vietnam.

The current approval process for clinical research protocols

When a protocol has been jointly developed by the principal investigator (PI) and the sponsor of the study, it is sent to the MOH's Department of Science and Training (DST) for review by the Ethics Committee and the Science Committee, and eventually approved. DST coordinates the process of reviewing protocols, monitoring trial implementation, and evaluating trial results as well as providing guidance.

Regulations on clinical research protocols

Since the majority of clinical studies are 'multi-center' projects, protocol must follow a standard MOH format, clarifying actual procedures and written in either Vietnamese or English. It should include the following topics with additional documents, such as an investigator's brochure, submitted for reference only.

- letter of interest (format provided)
- a clinical research contract between the sponsor and the PI (format provided)
- trial design
- curriculum vitae of principal investigator and co-investigators
- a statement on ethical considerations
- a description of product(s)
  - » summary of findings from non-clinical studies
  - » summary of findings from pre-clinical studies
  - » summary of findings from clinical trials of the previous phases
- a report from the committee at the institutional level on scientific and ethical aspects of the trial
- samples of trial product(s), provided in the smallest possible packaging unit
- For protocol on clinical trial Phase 4, include Free Sales Certificate (FSC) or Certificate of Pharmaceutical Product (CPP), and Certificate of Good Manufacturing Practice (GMP).

Essential points

- Health institutes at the district level are not allowed to implement a clinical trial.
- Protocols must follow MOH format and be in either English or Vietnamese.
- Special ethical considerations should be given to trials on vulnerable groups.
- MOH responds within 60 working days of receipt of complete protocol documents.
- All revisions in the protocol should be approved by MOH prior to implementation. Minor amendments can be approved by DST while decisions on major changes should be made by the review committee.
- Review and approval of study results must be done at two levels, institutional and ministerial.
- Result should only be disseminated or published after being approved by the MOH review committee.

MOH must respond within 60 working days of receipt of complete protocol documents. Once approved, contents of a protocol must not be changed or revised without prior approval from the MOH-DST. However, current wording *"revising the MOH-approved protocol's contents is prohibited"* can create misunderstanding, and is therefore under review in the upcoming version.

Regulations on the qualifications of investigators

- The investigating organization should be qualified with the facilities, equipment, and human resources necessary to guarantee proper conduct and to comply with Good Clinical Practice (GCP). There should be no financial or organizational relationship between investigators and the sponsor outside of the study.
- Currently, only health institutes at the central level directly managed by MOH may conduct clinical trials. In Ho Chi Minh City (HCMC), provincial level hospitals can be investigators given prior approval from the Provincial Health Service (PHS).
- The PI should be a medical doctor with qualifications and clinical experience necessary to undertake the study, and should demonstrate the ability to work according to GCP guidelines and other relevant legislation. Participating investigators should have appropriate qualifications and be trained on current GCP knowledge and research skills.

MOH currently allows two approaches for selecting the investigating organization: (1) after approving the proposal, MOH suggests at least three eligible, domestic institutes, or (2) the sponsor directly contacts an institute and proposes them to MOH. In the latter, the Ministry reserves the right to reject the proposed institute.

Protection of study participants

- Study participants should be voluntary, suitable for the study, and competent in civil behaviors.
- Participants or their guardians should give informed consent.
- An ethics committee must give special consideration to protecting the welfare of special participants, such as children, pregnant women, people with mental disabilities, people living with HIV/AIDS (PLHA), prisoners, detainees, and other special populations. The Minister of Health must approve all trials involving these populations.

Budgeting

- Budgets for clinical research should be presented in the contract in the provided format covering fees for review, approval, management, monitoring and evaluation.
- In government-sponsored research projects, budgets for clinical trials may be included in the original total budget, or provided separately by the organization.
- Investigating organizations and the PI are responsible for managing their budgets.

Quality Assurance

Quality assurance can be performed in three ways

- by the monitoring and evaluation working group appointed by the MOH through routine and unscheduled visits
- by the monitor(s) appointed by the sponsor
- by the ethics committee

Review and approval of results

Research results should be reviewed according to current regulations for research projects at the ministerial and institutional levels. For trials conducted by provincial institutions in HCMC, results should be reported to, but not reviewed by, the PHS.

The way forward for 2007 to 2010

MOH is in the process of developing guidelines for best practices in clinical trials and in training investigators and clinical research associates (CRA). DST is also developing and piloting GCP standards and establishing a data management system in collaboration with the MOH's Drug Administration Department (DAD).

Ethical aspects of biomedical research

Nguyen Ngo Quang, MSc.
Department of Science and Training, Vietnam Ministry of Health

Ethical principles

Ethics is one of the most ancient concepts in human society. Since the time of Hippocrates—or of Hai Thuong Lan Ong in Vietnam—protection of patients has been a chief concern in medicine. Ethical issues in biomedical and public health research are clearly of great importance, as any health care team involved in research is ethically bound to respect the patient or human subject. Good research requires that researchers respect the rights of their subjects, listen to and share information with them, and treat them courteously and caringly.

Essential points

- All biomedical research conducted in Vietnam, including postgraduate projects, requires ethical review.
- The Ethics Committee operates at two levels, institutional and ministerial, and represents different areas of expertise.
- Investigators submit the protocol proposal to the DST, who will then send it to the Ethics Committee for review.
- The Ethics Committee advises the Minister of Health on ethical considerations, and takes decisions through voting.
- The committee is currently responsible for initial review only. Its role in continuing review of ongoing research is still weak.
- Regulation No. 5219/BYT-QD, December 2002, details the organizational structure and operations of the ethics committee.

While *"ethics"* refers to a set of moral principles governing human character and conduct, traditionally the principles of *medical ethics* embrace the principles of **autonomy, beneficence** (do good); **non- malfeasance** (do no harm), and **justice**. These principles are as much relevant to biomedical research as they are to healthcare.

International guidelines for research on human subjects

- 1947: the Nuremberg Code—but does not mention clinical trials
- 1964: the World Medical Association Declaration of Helsinki—underscored 12 basic principles for the conduct of human biomedical research
- 1980, 1983, 1989, 1996 and 2000: the Helsinki Guidelines revised
- 1982: the Council for International Organization of Medical Sciences (CIOMS) proposed guidelines for international research. These were amended in 1993 and 2002 as the *International Ethical Guidelines for Biomedical Research Involving Human Subjects.*

Important requirements for ethics in biomedical research

- **Evaluating benefits and risks:** ensures that a subject's rights are respected, benefits are enhanced and risks are minimized, and participating groups are receiving the benefits and bearing the risks equally.
- **Obtaining informed consent:** ensures that participants decide, and then only after being fully informed on what the research is about, possible

benefits and risks, confidentiality, and incentives. Although consent must be obtained in writing, a signed consent form alone does not constitute informed consent.

- **Ensuring personal confidentiality:** participants' personal information must be respected and kept confidential.
- **Research involving vulnerable communities carries additional responsibilities:** special considerations must be paid to groups such as children, pregnant women, prisoners, detainees, people with mental disabilities, the poor, minorities, the illiterate, people living with HIV, men who have sex with men, sex workers, and others.

Ethical practice in biomedical research in Vietnam

Ethics committees

In Vietnam, the procedure for clinical trials requires that MOH establish an ethics committee to review and evaluate the ethical aspects of biomedical research. This is to safeguard the rights, safety, and well-being of all human subjects in a clinical trial. MOH regulation No. 5129/BYT-QD requires all biomedical research, including epidemiological surveys, to be reviewed by an ethics committee.

The committee can be at two levels, institutional and ministerial. An institutional committee has a term of four years and provides for seven members. A ministerial committee has a term of five years and provides for nine members. Committee members should have different qualifications and experience to represent many areas of medicine, and must include a lawyer and the chair of the Healthcare Labor Union.

Currently the ethics committee in Vietnam is primarily responsible for

- organizing and conducting reviews of protocol
- notifying the investigator/institution about research-related decisions and issues where they have concern

The monitoring role of the ethics committee in Vietnam has not been a priority in recent years but the government has plans to strengthen this. Currently the DST oversees investigators and study protocols.

The ethics committee in Vietnam is appointed by MOH and therefore not completely independent of the government. It reviews protocols and advises the Minister of Health on the ethical aspects. The Minister of Health has the ultimate say in decisions to approve or reject a proposal.

Organizational structure and operational guidelines for the ethics committee at both levels are detailed in MOH regulation No. 5129/BYT-QD, issued in 2002. Each institution or organization will have its own guidelines on organizational structure and operation of its own ethics committee, as well as guidance on procedures for appeal of regulations.

For ethical review

For review, the ethics committee needs

- a letter requesting approval
- a copy of the research protocol
- curriculum vitae of principle investigator and co-investigator(s)
- the information form to be provided to participants
- written informed consent forms
- a statement of adherence to ethical requirements and any agreement with participants set forth in the consent form and information form

Review procedures

- determine the adequacy of the proposed protocol according to ethical concerns and law
- committee members review proposal and, if necessary, non-members with expertise, before committee's bi-weekly meetings
- review meeting including discussion
- vote on approval

- notification of the committee's decision, issues and questions
- continuing review of the ongoing research

Questions and discussion

Biomedical research under postgraduate courses: Attendees at these proceedings raised the question of ethical review for biomedical research conducted as partial fulfillment of a postgraduate degree, particularly in non-medical universities. Dr. Quang from the DST-MOH responded that theoretically all biomedical studies require ethical review regardless of the context. In fact, the Ethics Committee is currently only operating at the Hanoi Medical University and HCMC Medical and Pharmaceutical University, and generally review applies only to students of these two universities. At other universities, biomedical research may not undergo the ethical review process because there may be no ethics committee, because postgraduate theses are managed by the Ministry of Education and Training (MOET), or due to lack of coordination between MOH and MOET.

Current practice of the ethics committee: Other attendees raised questions about whether there is only one ethics committee to review all protocols during the five-year term or whether a committee is newly established whenever a new protocol is submitted. Dr. Quang responded that the ethics committee must review all new protocols during its term. But current practice has been less than the standard following the deaths of the Chair and the Vice-chair during the 2002–07 term. A new committee will not be established until the new term starts, and in this transition period the Minister of Health will appoint an ethics committee for each protocol. MOH has also proposed one new branch of the Ethics Committee in HCMC so that proposals in southern areas can be reviewed in a prompt manner.

Participants then asked about voting and evaluation: The ethics committee makes its decision through voting. A decision needs a two-thirds majority to pass. Decision follows three levels: (1) accepted without amendment (2) accepted with minor amendments, and (3) not accepted. If approved it is then presented to the Minister of Health for final approval.

Good Clinical Practice

Nguyen Ngo Quang, MSc.
Department of Science and Training, Vietnam Ministry of Health

The purpose of this presentation is to provide an overview of good clinical practice (GCP). This includes concepts, goals, principles, activities, and phases of clinical trials, as well as World Health Organization (WHO) GCP guidelines and their current use in Vietnam. MOH is also developing a first edition Guidelines for GCP in Vietnam, planned for late 2007.

What is Good Clinical Practice?

Good Clinical Practice (GCP) is an international scientific and ethical quality standard for designing, conducting, recording, and reporting on clinical research involving human subjects. The ICH Harmonized Tripartite Guideline for Good Clinical Practice (E6) is the latest such standard approved by the U.S. Food and Drug Administration (FDA).

Essential points

- GCP is an international scientific and ethical standard for designing, conducting, recording, and reporting on clinical research that involves human subjects.
- Clinical research should comply with basic ethical principles in ICH E6.
- Responsibility for GCP is shared by all parties involved including sponsors, investigators, CROs, ethics committees, authorities, and subjects.
- Vietnam GCP is planned for publication in late 2007. Currently, ICH Guidelines provide detailed guidance on roles, responsibilities, and essential documents for the protocol.

Why GCP?

The purpose of GCP is to ensure that clinical research conducted on human subjects is designed and conducted according to sound scientific and ethical standards. Compliance assures that the rights, safety, and well-being of subjects are protected, the clinical research data are credible, and quality assurance systems are functioning well.

GCP Principles

GCP Principles reflect the Declaration of Helsinki, the Nuremberg Code, the CIOMS, and WHO Guidelines on Good Clinical Practice, as well as other recognized conventions.

1. **Ethical conduct:** Clinical research should be conducted in accordance with basic ethical principles, namely respect for persons, beneficence, and justice, which permeate all other GCP principles.
2. **Risk-benefit assessment:** A risk-benefit analysis of the study should precede the research itself.
3. **Weighing risk and benefits:** A research study should be initiated and continued only if the anticipated benefits for the individual subject and society justify the risks, especially the risks related to the safety and well-being of human subjects.
4. **Compliance with protocol:** A research study should be conducted in compliance with protocol that has received prior approval and receives ongoing oversight while an active protocol from an ethics committee and institutional review board.
5. **Supporting documents:** Review and approval of the clinical research study should be adequately supported by available non-clinical and clinical information.

6. **Protocol:** Clinical research should be scientifically sound and described in a clear and detailed protocol.
7. **Informed consent:** Voluntarily informed consent should be obtained from every subject, or guardian in case the subject is not mentally or legally capable prior to participation.
8. **Investigator qualifications:** Investigators giving medical care to subjects must be qualified physicians, even if the subject has decided to withdraw from the research.
9. **Staff qualifications:** Each individual conducting research should be qualified with proper education, training, and experience, and should be licensed, if necessary, to perform required tasks.
10. **Records:** All clinical data should be recorded, handled, and stored in a manner that allows for accurate reporting and interpretation.
11. **Confidentiality and privacy:** Human subjects' personal information and study records must be kept confidential. Respect for privacy and confidentiality are integral parts of these regulatory requirements and are universal.
12. **Good Manufacturing Practice (GMP):** Products developed from or used in research should be manufactured, handled, and stored in accordance with applicable GMP guidelines and should be used in accordance with the approved protocol.
13. **Quality systems:** Procedures must assure the quality of every aspect of clinical research.

Phases in clinical research

The development of new medical products (i.e., medicine, vaccine, equipment) involves

- **Pre-clinical phase:** conducted on animals, studies biomedical characteristics, toxicity, and in some cases dosage
- **Phase I:** tests the product in a small group of people for the first time to determine safe dosage, identifies side effects, and evaluates product safety
- **Phase II:** continues testing on a larger group to further evaluate toxicity, dosage and also efficacy
- **Phase III:** involves randomized controlled trials on large groups, often multi-center, offering a definitive assessment of how effective the product is; research results provide scientific evidence which, together with previous results, is submitted to regulatory bodies for review and approval for marketing
- **Phase IV:** follows product approval and marketing, to gather information on effects in various populations and side effects associated with long-term use.

Currently, MOH does not provide an exact figure for number of human subjects required for each phase, as this depends on the nature of the product and protocol.

Main contents of the ICH Guidelines on Good Clinical Practice

1. **Glossary**
2. **The Principles of ICH GCP:** 13 above-mentioned principles
3. **Independent Ethics Committee (IEC):** responsibilities; composition; function; and operations
4. **Investigators:** qualifications; available resources; medical care of research subjects; communication with IEC; compliance with protocol; investigation product(s); randomization procedures and unblinding; informed consent from subjects; records and reports; progress reports; safety reporting; termination or suspension of research; final report
5. **Sponsor:** quality assurance and quality control; contracted research organization; medical expertise; research design; management; data handling and recordkeeping; selection of investigators; allocation of responsibilities; compensation to subjects and investigators; financing; notification/submission to regulatory authorities; confirmation of review by IRB/IEC; information on investigational product(s); manufacturing, packaging, labeling and coding investigational product(s); access to

records; safety information; adverse drug reaction (ADR) reporting; monitoring; audits; non-compliance; premature termination and/or suspension of research; multi-center research

6. **Clinical research protocol and protocol amendments:** general information; background information; research objectives and purposes; research design; selection and withdrawal of subjects; treatment of subjects; assessment of efficacy; assessment of safety; statistics; direct access to source data/documents; quality control and quality assurance; ethics; data handling and record keeping; financing and insurance; publication policy; and supplements
7. **Investigator's brochure:** introduction; general considerations; contents of the investigator's brochure; Appendices 1 and 2
8. **Essential documents for the conduct of clinical research:** introduction; period before clinical phase commences; during the clinical research; after completion or termination of research

Questions and discussion

Compensation for subjects: Attendees asked how much is enough compensation for research subjects without affecting the voluntary nature of their participation. MOH responded that is not responsible for specifying the amount of compensation (this is the role of the Ministry of Finance (MOF) and there is currently no guideline. It is the matter of negotiation between investigator(s) and participants and dependent on the nature of the research. However, the compensation, method, and manner, as well as other benefits for subjects, should be clarified in advance an information form.

Overlap in responsibilities of regulatory authorities: Attendees raised the issue of overlapping responsibilities between different departments at MOH. Dr. Quang responded that currently the DST is responsible for technical and ethical review while the Department of Finance is in charge of the financial aspects of the protocol, and funding procedures are reviewed by the Department of Planning. Ministry leadership on allocation of tasks, however, is not clear and could be interpreted differently by each department. This creates complicated and overlapping procedures for investigators during the approval process, particularly for research with international cooperation. It is now the role of the MOH to detail and clarify responsibilities and the scope of review for each body.

Guidelines for review and evaluation of protocols

Nguyen Ngo Quang, MSc.
Department of Science and Training, Vietnam Ministry of Health

This presentation reviews the international guidelines for the ethical and scientific evaluation of clinical research. It is based on close examination of well-established guidelines, including WHO Operational Guidelines for Ethics Committees that review biomedical research, and the WHO and ICH Guidelines for GCP, as well as the few existing regulations on clinical research in Vietnam. These guidelines are intended to facilitate and support the current review process in Vietnam, to develop consistent national guidelines for the ethical and scientific review of clinical research.

General requirements

Following are the four main elements in the review of research proposals and their supporting documents. In addition, review committees need to take into account the requirements of applicable laws and regulations.

- ethics and safety for research subjects and researcher(s)
- scientific relevance and value of the clinical study
- research methodology
- feasibility of the research itself and quality assurance

Ethics and safety

Evaluation of protocol should involve the following questions:

- Has it been reviewed by an appropriate ethics committee?
- Have research teams obtained information on subjects and informed consent in writing?
- Have researchers confirmed confidentiality?
- What are the main considerations in product safety, risk to subjects, product efficacy, monitoring of product effectiveness and tolerance during the study, as well as follow-up after research?

Scientific and medical values

This process must consider potential for the use of results, the previous similar research, recruitment of study participants, treatment, and follow-up. Checklists include

- Is this research necessary (e.g., not repeating a previous study)?

Essential points

- International guidelines for review and evaluation of a clinical study proposal are intended to facilitate and support the current review process in Vietnam.
- Four main elements are recommended for review of research proposals: ethics and safety; scientific relevance; research methodology; and research feasibility.
- Detailed guidelines for ethical review are available but scientific review guidelines are still in development.

- Are there inclusion and exclusion criteria?
- Are treatment regimens for subjects appropriate?
- Is the follow-up and medical care provided adequate?
- Will the outcomes (e.g., suitability, feasibility, international acceptability) be measured and are these appropriate?
- Are the recording procedures for adverse effects appropriate?

Research methodology and bias

- Are the selected methods (e.g., clinical trial, cohort study, case-control study) suitable to the research topics?
- Is there an acceptable calculation for required sample size? Are the prognostic biases caused by the withdrawal of research subjects considered?
- Are exclusion criteria accurate, valid, and justified?
- Are suspension and termination criteria well defined and acceptable?
- Is the plan for data analysis clearly described?

Feasibility

Investigators should also prove that they are capable of carrying out research with sufficient infrastructure and staff, specifically

- Is the investigating organization strong in the recruitment and provision of care and follow-up for research participants?
- Will the products be managed according to the plan?
- Will the outcomes be measurable?
- Are the experiments technically appropriate?
- Are the data collection methods and treatment procedures appropriate?
- Will the clinical trial be sufficiently supervised and monitored?
- Will there be sufficient follow up for subjects?

Questions and discussion

Impartiality and partiality among EC members: A participant raised a doubt about the relevance of evaluation from EC members. The ethics committee in Vietnam does not always represent a variety of perspectives, but merely a scientific view. Their comments and evaluations are often focused on the technical rather than the ethical aspects. Dr. Quang from the DST responded that though the guidelines are available, the EC does not always fully understand or follow them. But MOH has a plan to train and re-train members on the principles and guidelines for ethical review of research protocols in the near future.

Guidelines for scientific review: Attendees also asked whether there were as detailed guidelines for scientific review as there are for ethical review. Dr. Quang responded that detailed guidelines are being prepared by the DST. At the ministry level, two different protocols have been prepared for two review processes: scientific and ethical. Thus there is less confusion at this level. However, the two committees at the institutional level may still need training or re-training, which MOH hopes to provide in the near future.

Guidelines for review of pre-clinical research protocols: Attendees noted the lack of guidelines for reviewing protocols in the pre-clinical phases. The presenter responded that before January 2007, Decision No. 371 BYT-QD regulated all pre-clinical and clinical research processes. And Decision No. 01 replaced the previous regulations on all items related to clinical research in January 2007. The pre-clinical research process, however, still does not adhere completely to Decision No. 371 and new regulations are in the process of development.

Attendees also asked whether it is necessary to conduct pre-clinical trials for drugs that cannot be tested on animals. This revealed a misunderstanding, as pre-clinical trials could be animal or laboratory-based. Ultimately all clinical trials require study results from the pre-clinical phase.

Guidance for different categories of clinical research: The audience further asked whether MOH has detailed policy on specific types of clinical research, as many aspects and procedures are not the same across trials. Dr. Quang responded that since the law defines the term "medicine" as covering both medicinal drugs and vaccines, the regulation on clinical research (Decision No. 01) cannot separate them. Regulations, therefore, are still vague and difficult to implement. But MOH plans to issue detailed guidelines for specific categories of clinical research, which likely won't be included in regulatory documents.

Plan for GCP implementation: 2007–2010

Nguyen Ngo Quang, MSc.
Department of Science and Training, Vietnam Ministry of Health

Biomedical research is becoming increasingly important in Vietnam and a more comprehensive, more stringent regulatory environment for scientific and ethical standards will follow. From 1996 to 2002 MOH developed its first regulations on clinical research, yet there are many more that need to be implemented by 2010. Funding is the major impasse and MOH will mainly depend on international aid for training of clinical research personnel. And this training must comply with MOH guidelines.

Objectives of MOH's GCP plan

- To increase knowledge and skills of investigators, monitors, supervisors, managers and review committees in GCP and ethics in clinical research.
- To establish a monitoring and evaluation (M&E) system for clinical research in accordance with GCP standards.
- To establish a network of investigating organizations meeting GCP requirements in conducting clinical research.
- To develop a data management system for clinical research.

Although these four objectives will be implemented simultaneously over the next three years the first remains the most important, as it concerns the personnel aspect. Strengthened capacity of people involved in GCP will result in better implementation, monitoring, and management.

Proposed activities

Objective 1: *Increase knowledge and skills of investigators, monitors, supervisors, managers, and members of review committees in GCP and ethics in clinical research.*

- Issue the GCP Guidelines of Vietnam (September 2007).
- Establish the ethics committee for the new term (2007–2012).
- Conduct trainings and provide MOH certificates on GCP.
- Complete a GCP training package comprised of GCP guidelines and other regulatory documents.
- Increase collaboration between MOH and international organizations (NGOs, pharmaceutical companies).

Objective 2: *Establish an M&E system for clinical research in accordance with GCP standards.*

- Develop M&E tools and protocols.
- Train monitors at the national and institutional levels.
- Conduct routine M&E by the ethics committee, national monitors, sponsors, and managerial bodies.

Objective 3: *Establish a network of investigating organizations meeting GCP requirements in conducting clinical research.*

- Develop criteria and tools for reviewing and evaluating investigating organizations.
- Disseminate these evaluation criteria and tools so that investigating organizations are well informed for their preparation.
- Review, evaluate, and grant the GCP certificate for eligible organizations.
- Support DST and standardized investigating organizations with equipment for data management and for GCP trainers.

Objective 4: *Develop a data management system for clinical research.*

- Develop protocols for management and storage of clinical research.
- Develop a computer system for data management (currently paper-based).
- Provide training for data management personnel on applying the new system.
- Pilot a new management system for clinical research data.

Procedures for manufacture and import of medicinal drugs for clinical research

Dr. Do Minh Hung
Drug Administration Department, Vietnam Ministry of Health

Any medicinal product used for clinical research must receive approval from the Drug Administration Department for production if locally produced or for import if donated. The application is due after the clinical research protocol has been reviewed by the science and ethics committees and approved by MOH.

In Vietnam, "medicinal drug" is understood as including pharmaceuticals and other biomedical products. Drugs and medical biological products used for clinical research must be manufactured at GMP-qualified facilities. If a facility (e.g., a hospital) does not have the GMP certificate, it should be evaluated by MOH prior to approval of the application. The sponsor, investigating organization, or an officially-designated organization may submit the application.

Essential points

- DAD must approve import or manufacture of study drug or biological product.
- Written approval for research protocol should be obtained from the DST prior to the application for manufacturing/import.
- Application dossiers should comply with regulations and vary according to product as follows
  - » Pharmaceutical products: locally produced or imported/donated
  - » Vaccines/biological products
- Packaging, coding, and labeling of products should comply with regulations for drugs and vaccines while ensuring the trials remain 'blind'.
- Destruction of products should strictly follow guidance for specific types of drugs.

Pharmaceutical products

An applicant must submit the following documents to DAD for review. Upon obtaining written permission (due in five to seven working days), the organization is entitled to produce, receive, or import the study pharmaceutical for clinical trials.

Locally-produced drugs: per Decision No. 3121/2001/QD-BYT on Drug Registration, the application should include

- a letter of request for manufacturing
- product specifications, analytical methods, and analysis prepared by the manufacturer (if the manufacturer is GMP-certified) or the national analytical institution
- manufacturer's protocol: a list of all components and the quantitative composition of the investigational product (active ingredients only), a description of manufacturing method and procedure, as well as a list of equipment and facilities used to produce this product
- labeling indicating the quantity for each packaging unit
- an approval letter from MOH for the clinical research protocol (original copy or a photocopy certified by the investigating organization)

Donated drugs: per Circular No. 06/2006/TT-BYT on import and export of drugs and cosmetics

- a letter of request for receiving donated drugs for clinical research
- a list of donated drugs (format provided)
- an approval letter from MOH for the clinical research protocol (original copy or a photocopy certified by the investigating organization)

Imported drugs: per Circular No. 13/1998/TT-BYT on receiving, management, and use of donated drugs

- a letter of request for import of drugs used for clinical research
- completed customs form for import
- approval from MOH for the clinical research protocol (original copy or a photocopy certified by the investigating organization)

Vaccines and medical biological products

DAD receives applications to use/import vaccines and medical biological products. Upon written approval from DAD—due in seven working days for locally-produced products and 15 working days for imported products after receipt of the dossier—the organization is eligible to produce, receive and import vaccines or biomedical products for clinical trials. The following documents must be included in the application.

Locally-produced vaccines and medical biological products: per Decision No. 4012/2003/QD-BYT on Vaccine and Medical Biological Registration

- a letter of request for production
- specifications and analytical methods
- analysis report
- description of manufacturing processes, methods, and quality assurance methods
- labeling
- written approval from MOH for the clinical research protocol (original or certified copy)

Imported vaccines and medical biological products: per Circular No. 08/2006/TT-BYT on import of vaccines, biomedical products, chemicals, medical equipment, antiseptics, and disinfectants for domestic and medical use

- a letter of request for import
- written approval from MOH for the clinical research protocol (original or notarized copy).

Packaging, labeling, and coding of investigational product

- Vaccines and medical biological products
- Products for investigation should be packaged to prevent contamination and deterioration during transport and storage.
- Labeling should comply with Vietnamese regulations. In addition, products should be labeled and coded in a manner that protects the process of blinded trials.
- In blinded trials, the coding system for products should include a way to identify if the subject is receiving study product or placebo (or other treatment) in case of medical emergency, but does not permit any study investigator or the subject to discover if the drug given to the patient is an active study drug or placebo.

The product label should include

- name of the product
- name and address of the manufacturer
- composition
- indications, uses, contra-indications if applicable
- product presentation
- packaging form
- batch number, expiry, storage conditions, manufacture date
- precautions (indications)
- printed note: *"This product is for clinical trial only. Use for other purposes is prohibited."*

Destruction of products for investigation

At the conclusion of clinical study, investigated products will either be returned to the sponsor, destroyed, or recycled after obtaining written permission from DAD. This must comply with regulatory requirements, particularly for controlled drugs such as toxics, narcotics, and psychotherapeutics. Safety and protection for humans, animals, and the environment must be ensured.

Destruction of investigated products must be carried out upon written decision from the sponsor and under witness of a minimum three-person board specifically for that purpose. Upon completion this panel should complete a report for submission to the regulating body.

Questions and discussion

Labeling in blind research: Participants asked how to declare imported products to customs if the label is blind and the importing organization cannot identify the active comparator(s) and the placebo. Dr. Hung from DAD responded that the importing organization should be able to declare the quantity of each category but does not need to indicate which packaging unit is the active product and which is the placebo.

Different labeling between the protocol and the application: One participant asked about the situation when the import application mentions the generic name of the drug while the clinical trial uses the brand name. Dr. Hung suggested the applicant revise the dossier to make it consistent or to provide written confirmation to explain this difference.

Pharmacovigilance and reporting of adverse drug reactions

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Pharmacovigilance is the recording, reporting, and analysis of adverse events in relation to the use of medicines. It has been estimated that such adverse drug reactions (ADRs) are the fourth largest cause of mortality in the USA, and this figure could be higher in developing countries. The aims of pharmacovigilance are to enhance patient care and safety and to improve public health and safety with medicines by providing reliable information. This includes hospitals and academia, health professionals, the pharmaceutical industry, authorities, the media, and patients in detecting and reporting adverse events. Pharmacovigilance is promoted at the country level by the WHO in collaboration with the Uppsala Monitoring Center, of which Vietnam is a member.

Essential points

- Reporting on adverse events and side effects related to the use of medicines or treatment is crucial to ensure patient safety and public health.
- There are different types of adverse drug events. ADR reporting in clinical research focuses on ADRs that are both serious and unexpected.
- Current regulations in Vietnam require compulsory ADR reporting by companies and manufacturing organizations. There is no regulatory requirement for research and treatment.
- Investigators are encouraged to report ADRs during the course of clinical trials, independently from ADR reporting by the sponsor.

Among other things, monitoring of ADR helps regulatory bodies to approve clinical trials and to make prompt decisions on premature termination or suspension of trials.

ADR reporting in Vietnam

While strongly promoted in developed countries, ADR reporting, especially in clinical trials, has not been prominent in Vietnam. Since its establishment in 1994, the Vietnam ADR has only received reports for the post-marketing phase in trials and not for actual trial phases. The National ADR Center operates as an independent institute and is totally dependent on foreign financial support. This makes it difficult for the center to be actively involved in processing and making decisions about reported ADRs.

Starting in 2006, ADR reporting by pharmaceutical and other commercial companies is compulsory but there is no requirement for research and treatment facilities, such as hospitals. The current approach to ADR reporting in clinical research in Vietnam is for encouraging investigators only, and does not establish any legally enforceable responsibilities. Recommendations focus merely on situations when the investigated product may pose a clinically important or unexpected risk.

The following may therefore be used as a reference for investigators in reporting ADRs during the clinical research.

Glossary

An **adverse drug reaction (ADR)** is a response to a medicine which is noxious and unintended, and occurs at doses normally used in men.

An **unexpected adverse reaction** is a reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or with expected characteristics of the drug.

A **side effect** is any unintended effect of a pharmaceutical product occurring at doses normally used by a patient, related to the pharmacological properties of the drug.

An **adverse event** is any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with the treatment under investigation.

A **serious adverse event** is any event that is fatal, life-threatening, permanently or significantly disabling, requires or prolongs hospitalization, or causes a congenital anomaly.

Evaluating ADR- drug/treatment causal relationship

The causal relationship between an ADR and the treatment/drug can be evaluated according to six levels of possibility:

1. certain
2. probable/likely
3. possible
4. unlikely
5. conditional/unclassified
6. unassessable/unclassifiable

Identifying the level of causal relationship between an adverse event and the treatment, the severity of the event, and the frequency of its presence is critical for investigators in reporting on the adverse event and for regulators in making decisions about the continuity of the treatment or research.

What should investigators report?

Investigators and sponsors should report all suspected adverse reactions that are considered "likely" associated with the trial, and those of clinical importance, with an emphasis on ADRs that are serious and unexpected.

While almost all international sponsors have independent monitoring committees to oversee compliance with the approved protocol and adverse events—and while sponsors must report ADRs—investigators submit their own report on reactions that may emerge during the course of clinical trials in order to avoid misleading data due to conflict of interest.

How to report ADRs

An ADR Report Form covers four sections on patient information, adverse events and product problems, suspected medications, and reporter information. The completed report should be sent to the National ADR Center in Hanoi or its office in HCMC, either by post, email, or facsimile. Feedback from the ADR Center is free of charge.

Procedures for processing ADR reports

The National ADR Center classifies reports according to drug category. A consultation group will meet to review and evaluate cases. They will then give their conclusions to the reporting body and to the Uppsala Center. Due to funding shortfalls, this consultation group holds review meetings every six months, but conducts actual reviews within one week, passing on feedback to investigators and regulatory bodies on ADRs that are both serious and unexpected.

Review and approval of foreign, non-government sponsored projects

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Foreign funding in general, and foreign non-governmental (NGO) aid in particular, play an important role in the development of Vietnam and the health care sector is no exception. The Government of Vietnam has issued regulations for reviewing and approving foreign NGO-sponsored project proposals and the purpose of this presentation is also to provide an overview of these procedures.

Regulations on non-government aid

- Decision No. 64/2001/QD-TTg on the management and use of foreign non-governmental aids
- Circular No. 04/2001/TT-BKH on implementation of Decision No. 64/2001/QD-TTg
- Direction No. 11/2002/CT-TTg strengthening management and use of foreign non–government aid
- Decision No. 1829/2002/QD-BYT by the Ministry of Health on management and use of non–government aid in the health sector

Essential points

- Clinical NGO research must have approval for receipt of funds in addition to approval for research protocol.
- NGO aid requires approval at the governmental, ministerial, departmental or provincial level depending on scale.
- Review involves several ministries or MOH departments. Implementing agencies should
  - » prepare proper documents with sufficient information
  - » apply for approval and receipt of aid at the same time
  - » All details (drug names, quantities) must be consistent across proposal documents.

On approval

The Prime Minister (PM) is responsible for ratifying

- programs and projects using NGO aid valued at US$ 500,000 or above
- non-project aid valued at US$ 200,000 or more
- non-project aid involving items that have been in use (except for goods imported as non-trade)

The Minister of Health is responsible for approving

- programs and projects of US$ 200,000 to 500,000
- non-project aid under US$ 200,000, except for used goods and equipment

Heads of the ministerial departments will approve

- programs and projects under US$ 200,000

Chairs of the provincial People's Committees will approve

- programs and projects under US$ 500,000 and funded directly for a provincial agency—

MOH will provide technical assistance in the review process

- non-project aid valued at under US$ 200,000, except for used goods

Review and approval process

- The Department of Planning and Finance is the focal point for receiving proposals.
- The proposal is reviewed by specific departments within MOH.
- All comments are compiled and communicated to the applicant.

The revised proposal is submitted to the Minister of Health (or Deputy Minister) for approval, or in case the proposal requires Prime Ministerial approval it is sent to the Ministry of Planning and Investment (MPI) to be reviewed and submitted to the PM for ratification.

Content and format

Proposals should consist of

- letter of request for approval from the implementing agency
- project/program proposal
- initial project/program proposal submitted by the implementing agency and accepted by the sponsor
- written agreement by the sponsor to fund the project
- a memorandum of understanding or agreement between the sponsor and implementer
- a copy of the permit for international NGOs (INGO) working in Vietnam, issued by the People's Aid Coordinating Committee (PACCOM)
- Supplementary documents, if any, including
  - » protocol approval by the direct managing authority
  - » approval by the EC
  - » written agreement by participating organizations
  - » written agreement by local authorities (Provincial Health Service or Provincial People's Committee)
  - » expense norms in agreement with the sponsor
  - » copy of registration for drug(s) or medial biological products in Vietnam or other countries.

The project proposal should include

- cover page
  - » title and code of the project
  - » place(s) of implementation
  - » implementing agency name and contact information
  - » total funding including investment capital and reciprocal capital
  - » timeframe.
- summary of the project (1 page)
- rationale
- goals and objectives
- expected outputs
- activities
- budget (including detailed budgets)
- implementation plan
- cost-effectiveness analysis of financial, social, environmental, and sustainable issues.

State management over review and approval of foreign non-governmental aid

- The MOH Department of Planning and Finance reviews and approves budgets and expenditure norms and financial reports.
- The MPI Department of Foreign Economic Relations reviews and submits the proposal to the PM for final ratification.
- The MOF's Department of External Finance reviews the sponsoring process and submits the proposal to the PM for approval for receiving foreign NGO aid.

- The Vietnam Union for Friendship Organizations (VUFO) and PACCOM issue the Permit for INGOs working in Vietnam and compile project reports from INGOs.

Reporting requirements

The sponsor and the implementing agency should submit financial reports to MOH DPF every six months and at the end of the project. Financial reports should consist of a receipt and management of aid, and a report on implementation of aid.

Common problems in implementation

- When implementation is delayed, the implementing agency may develop proposal documents before obtaining written agreement for funding from the sponsor. The agency may submit the proposal to the DPF before receiving approval from other ministerial agencies (DAD) for drugs and medical biological products used for clinical trials.
- Delays in approval. (Note that when project activities are implemented before approval, the implementing agency should not dispense any funds, since any funds spent before the approval date will not be reimbursed.)
- Delays in bidding, purchasing, and implementation plans.
- Delays in obtaining approval for project amendments.
- Duty-free goods are different from that listed in the aid proposal.
- Difficulties in obtaining import permits for drugs and medical biological products; the implementing agency should obtain written confirmation from DAD to use these prior to applying for import.
- Problems related to sponsor's working permit. In the case of an INGO in the process of renewing or extending the permit, written confirmation from PACCOM is necessary.
- Changes in project staff.

Questions and discussion

Technical approval and approval of aid: Attendees at the symposium asked about the potential overlap in roles between the DST and the DPF in reviewing and approving the clinical research, as their comments are sometimes similar. Mr. Nam from the DPF responded that there are two approval processes, for the trial itself and for the actual aid. But approval only is not sufficient for importing drugs and medical products. All technical review results must be attached to the proposal submission to avoid the repetition of review and comment.

Budget details: One participant presented a situation where the sponsor does not clarify the cost of a drug or treatment and questioned how that cost could be calculated. Mr. Nam responded that budget items for that drug are not necessarily precise, but can be estimated. However, the drug must be included in the proposal and budget before import. Actual costs will be confirmed based on original invoices and receipts once the imported goods arrive.

Who is the sponsor? Funding can either be governmental or non-governmental and from different international organizations. However, only the organization which directly transfers the funds to Vietnamese agencies is considered the "sponsor", and is required to have permits to operate in Vietnam.

"Program/project" versus "scientific research": In documents in Vietnamese, the term "scientific research" refers to a clinical trial itself and can be used in documents for scientific and ethical review. The term "program" or "project" should be used when mentioning funding issues.

Guidelines for financial management of foreign NGO funding

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General applications

- Foreign aid is considered a part of government funding and is managed and implemented according to the State Budget Law.
- Foreign NGO aid is received and implemented upon obtaining necessary ratifications.
- Only legal entities are eligible for receiving, managing, and spending foreign aid.
- Heads of implementing agencies are responsible for ensuring project/program objectives are achieved, proposed activities are implemented, and project budgets are managed and used in compliance with Vietnamese law.
- Implementing agencies should comply with the sponsor's requirements for purchasing, bidding, disbursing, financial management and reporting, auditing and reimbursement.

Development of project budgets

There are two budgets that need to be developed and approved, total project budget and fiscal year budget. Fiscal year budgets are developed based on the total budget and implementation plan, with certain factors affecting disbursement. Fiscal year budgets are approved annually.

- Budgets must reflect all funding sources for the project, including investment and reciprocal funding.
- Budgets must be estimated for all proposed activities, including monitoring and management.
- All budget items must be explained in a clear way.
- Budget items are generally allocated for transportation, stationery, conferences and training, and consultants.

Management and use of funding

Implementing agencies are responsible for approving and managing expenditures spent for project activities, in compliance with the approved total budget and yearly budgets. Expenses must be consistent with the norms agreed with the sponsor and approved by regulatory authorities. All expenditures require invoices or necessary documents according to Government and sponsor requirements.

APPENDICES

Appendix 1: List of presenters

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Appendix 3: List of regulations and guidelines on clinical research

(Available in Vietnamese)

1. Decision No. 01/2007/QD-BYT, January 2007 on issuing guidelines for clinical research
2. Decision No. 64/2001/QD-TTg, April 2001 on issuing regulations on the management and use of foreign non-governmental aid
3. Circular No. 04/2001/TT-BKH, June 2001 on implementation of Decision No. 64/2001/QDD-TTg to issue regulations on the management and use of foreign non-governmental aid
4. Circular No. 06/2006/TT-BYT, May 2006 on import and export of drugs and cosmetics
5. Circular No. 08/2006/TT-BYT, June 2006 on import of vaccines, biomedical products, chemicals, medical equipment, antiseptics, and disinfectants for domestic and medical use
6. Circular No. 13/1998/TT-BYT, October 1998 on receiving, management of, and use of donated drugs
7. Direction No. 11/2002/CT-TTg, April 2002 on re-organizing the management and use of foreign non-governmental aid
8. Decision No. 1829/2002/QD-BYT, May 2002 on the management and use of foreign non-governmental aids in the health sector
9. Decision No. 3121/2001/QD-BYT, July 2001 on issuing the regulation on drug registration
10. Decision No. 4012/2003/QD-BYT, July 2003 on vaccine and medical biological registration
11. Correspondence No. 4331/QLD-BYT, July 2006 guiding the reporting of ADR
12. Standard Operating Procedure (SOP) for collection, receipt, and processing of ADR
13. Standard Operating Procedure (SOP) for review and approval of non-registered drugs
14. Circular No. 116/2005/TT-BTC, December 2005 guiding the management and handling of assets of state funded programs and projects, upon their completion.

Glossary

Clinical Research Protocol: A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

Clinical Trial: A research study with human subjects to answer specific questions about new therapies or vaccines or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective.

Confidentiality: The act of holding secret all information relating to a person enrolled in a clinical trial and allowing access to that information only to limited parties for whom the person has granted permission for disclosure by way of informed consent.

Double-Blind Study: A clinical trial design in which neither the human subjects participating in the trial know their own assignment to the study product or placebo nor do the study personnel administering the experiment know which subjects among the group are receiving the experimental drug and which are receiving a placebo (or another therapy).

Data Safety Monitoring Board (DSMB): An independent committee composed of community representatives and clinical research experts, that reviews data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved early.

Good Clinical Practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data, reported results, and information are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Human Subject: A living individual about whom the investigator conducting research obtains (a) data through intervention or interaction with the individual or (b) identifiable private information as defined in the Code of Federal Regulations. Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Inclusion Exclusion Criteria: Medical and social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.

Independent Ethics Committee (IEC): An independent body (i.e., a review board or a committee, institutional, regional, national, or supranational) constituted of medical and scientific professionals and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial.

Institutional Review Board (IRB): A committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. (It is one form of an Independent Ethics Committee.)

Investigational Medical Product: a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

Investigator's Brochure: A compilation of the clinical and non-clinical data on an investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Investigational New Drug (IND): A new drug, antibiotic drug, or biological drug that is used in a clinical investigation.

Placebo: A placebo is an inactive pill, liquid, or powder that has no treatment value.

Preclinical Trials: Refers to the testing of experimental drugs in the test tube or in animals - the testing that occurs before trials in humans are carried out. There are some fields where preclinical trials cannot be done.

Principle Investigator: The person responsible for the conduct of the clinical trial at a trial site.

Privacy: The state of being free from unsanctioned intrusion, as in a person's right to privacy.

Quality Assurance: A system of on-site monitoring of clinical trial activity to assure that the rights and welfare of human research subjects are protected and that the performance of research involving human subjects meets the highest standard of quality and is in compliance with all applicable regulatory guidance.

Risk-Benefit Ratio: A comparison of the risk to individual participants with the potential benefits. The risk/benefit ratio may differ depending on the condition being treated and the population studied.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (i.e., original records or certified copies).

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and financing of a clinical trial (ICH). The government can be a sponsor.